Rhythms of the Brain

György Buzsáki

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To my loved ones.

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Prelude

> If the brain were simple enough for us to understand it, we would be too simple to understand it.
>
> —Ken Hill

The short punch line of this book is that brains are foretelling devices and their predictive powers emerge from the various rhythms they perpetually generate. At the same time, brain activity can be tuned to become an ideal observer of the environment, due to an organized *system* of rhythms. The specific physiological functions of brain rhythms vary from the obvious to the utterly impenetrable. A simple but persuasive example is walking. Bipedal walking is a periodic series of forward falls interrupted regularly by alternate extensions of each leg. It is almost as natural to us as breathing. This effortless exercise is made possible by the predictive nature of spinal cord oscillators. On smooth terrain, the alternation of leg movements can take us any distance. Perturbation of the clocking, on the other hand, signals a change in the terrain. This general mechanism is the same in all animals, including eight-legged scorpions and centipedes. The notion that oscillators or "central pattern generators"[1] are responsible for the coordination of motor

1. Neural circuits that produce self-sustaining patterns of behavior are called central pattern generators. The most studied central pattern generator is an intraspinal network of neurons responsible for locomotion. Grillner (1985) summarizes the pros and cons of the pacemaker view of central pattern generators in the spinal cord and brain. Stein et al. (1997) and Burke (2001) are nice updates on the topic. Central pattern generators are also responsible for many other types of rhythmic movements, e.g., peristaltic motor patterns of legless animals, rhythmic movement of the wings of crickets during song production, respiration, heart control, movements of the stomach, and other parts of the digestive system. My favorite review on this topic is Marder and Calabrese (1996).

patterns, such as breathing and walking, is old and well accepted in neuroscience. But the tantalizing conjecture that neuronal oscillators can be exploited for a plethora of other brain-generated functions, including cognition, is quite new and controversial. And it is the latter topic, the contribution of oscillations to the invisible, inferred operations of the brain, that this book is mostly about.

Exposing the mechanisms that allow complicated things to happen in a coordinated fashion in the brain has produced some of the most spectacular discoveries of neuroscience. However, I do not want to mislead you from the outset. Clocks are not thinking but ticking devices, no matter how precisely they can predict time. Time needs to be filled with content, provided by the appropriate firing patterns of neurons, whose assembly activity, in turn, is regulated by brain oscillations. Interestingly, the neuronal assemblies that generate the content are often the same as those that give rise to the time metric of oscillations that in turn organize the cell assembly pattern. This peculiar reciprocal causation, brought about by the self-organized features of brain activity, begs for an explanation. A good part of the volume is devoted to discussing experiments that attempt to elucidate these emerging properties of neuronal networks.

At the physiological level, oscillators do a great service for the brain: they coordinate or "synchronize" various operations within and across neuronal networks. *Syn* (meaning same) and *chronos* (meaning time) together make sure that everyone is up to the job and no one is left behind, the way the conductor creates temporal order among the large number of instruments in an orchestra. A close view of Seiji Ozawa at the end of a concert, sweat falling from his face, is proof that conducting an orchestra is a physically and mentally demanding job. In contrast, coupled oscillators perform the job of synchronization virtually effortlessly. This feature is built into their nature. In fact, oscillators do not do much else. They synchronize and predict. Yet, take away these features, and our brains will no longer work. Compromise them, and we will be treated for epilepsy, Parkinson's disease, sleep disorders, and other rhythm-based cognitive maladies. As I point out repeatedly in Cycles 1–13 of this volume, virtually no nervous function exists without a time metric, be it the simplest motor or the most complex cognitive act. While we know quite a bit about neurons, the building blocks of the brain, and have extensive knowledge about their connectivity, we still know very little how the modules and systems of modules work together. This is where oscillations offer their invaluable services.

My connection with brain rhythms began in April 1970, during a physiology lecture given by Endre Grastyán in the beautiful town of Pécs, on the sunny slopes of the Mecsek mountains in Hungary. The University of Pécs, or Universitas Quinque Ecclesiensis, as it was called when founded in 1367, has produced a remarkable set of neuroscientists, including János Szentágothai, the legendary neuroanatomist; Béla Flerkó and Béla Halász, pioneers of neuroendocrinology; György Székely, the renowned spinal cord physiologist; and Ferenc Gallyas, the creator of the silver impregnation methods widely used for neuronal labeling.

Like many of us at a young age, in his twenties Grastyán could not quite make up his mind about his future. Finding nothing too interesting or challenging initially,

he decided to train for the priesthood to get some orientation in philosophy. But his mind, far too curious and questioning, prevented him from becoming a preacher. He ended up in medical school during the stormy years after World War II and became the assistant of Professor Kálmán Lissák. Lissák, a student of Otto Loewi in Graz, Austria, and subsequently Walter Cannon's assistant at Harvard, had returned to Hungary to become Chair of Physiology just before the war. Grastyán's pairing with Lissák was fortunate because Lissák, of course, knew quite a bit about rhythms from his years with Loewi, who provided the first evidence that a chemical—a neurotransmitter—is released at the junction (synapse) between the vagus nerve and the heart muscle.[2] Although Grastyán was perhaps Lissák's closest friend, the two were as different as can be. Lissák was a reserved man, and his lectures were scarcely attended. In contrast, Grastyán was a performing artist whose seminars were carefully composed and choreographed. The huge lecture room in the medical school was always packed, and even students from the neighboring law school came over to listen to his mesmerizing lectures. He generated so much enthusiasm that we students became convinced that the topics he discussed were among the most important in the whole universe.

In that particular lecture of April 1970, he talked about how the brain outputs, such as movement and cognition, control its inputs, rather than the other way around. His key idea was that control in living systems begins with the output. This is the seed for further evolution of the brain. Even in the most complex animals, the goal of cognition is the guidance of action. Indeed, the first simple biological systems did not have any inputs; they did not need them. They simply used an economical motor output, a rhythmic contraction of muscles. This is, of course, is sufficient only when food is abundant in the sea environment. More complex forms of life evolved form this simple solution by modifying the simple rhythmic output. Sensation of direction and distance developed only after the "invention" of movement through space. The idea of output control and feedback is a profound thought even today. Back then, when Pavlovian sensory–sensory association was the dominant ideology in the East and the stimulus–decision–response paradigm dominated Western thinking, Grastyán's teachings were unusual, to say the least.

After his lecture, I rushed home to read the relevant chapters in our official

2. Loewi called the chemical "Vagusstoff," which Henry Hallett Dale from Cambridge, England, identified later as acetylcholine, the first neurotransmitter. They received the Nobel Prize for their discoveries in 1936. I have heard various versions of the story behind the Vagustoff experiment from Lissák. Here is one from Loewi's own pen:

> The night before Easter Sunday of that year I awoke, turned on the light, and jotted down a few notes on a tiny slip of thin paper. Then I felt asleep again. It occurred to me at six o'clock in the morning that I had written down something most important, but I was unable to decipher the scrawl. The next night, at three o'clock, the idea returned. It was the experiment to determine whether or not the hypothesis of chemical transmission that I had thought about years ago was correct. I got up immediately, went to the laboratory, and performed a simple experiment on a frog heart according to the nocturnal design. (Loewi, 1960, 15)

Dale became better known about his "principle": if a chemical is released in one synapse, the same chemical is released in all the other synapses made by the same neuron.

textbook only to realize that there was not a single word there about what I had heard that morning.[3] Nevertheless, beginning with Grastyán's introductory lecture on the organization of the brain, my life in medical school acquired new meaning. My original high school plan to become an electrical engineer was vetoed by my parents, who offered me the choice between medical school and law school. While my friends were having fun at the School of Engineering in Budapest, learning exciting stories about radio transmission and electronic oscillators, I spent most of my time studying the unending details of bones and ligaments. But in his physiology lecture, Grastyán was talking about some truly intriguing questions that sparked my interest. I applied to become his apprentice and spent most of my student life in his lab.

The best training in Grastyán's laboratory occurred through my participation in the regular lunch discussions that could go on for several hours, where topics meandered chaotically from homeostatic regulations of the brain to complex philosophical topics. It was during these lunch lessons where I first learned about the hippocampal "theta" rhythm, the oscillation that has become my obsession ever since. My first assignment in the Grastyán school, under the supervision of György Karmos, was to examine the variability of the evoked responses in the hippocampus and auditory cortex in response to sound stimuli as a function of behavior. In a nutshell, our main finding was that the most important factor in predicting the variability of the evoked brain responses was the variability of the background brain activity. This was the first time I faced the fascinating issues of "state," "context," and "spontaneous" activity, problems that remained with me forever.

As I have repeatedly discovered in my career, the informal lunch-seminar approach to science is hard to substitute with formal lectures or the reading of dense scientific papers. Seminars are tailored for an average group of people with the naive assumption that the audience retains all the details and follows and accepts the fundamental logic of the lecturer. In contrast, the essence of lunch conversations is to question the fundamental logic, a quest for clarification and simplification, a search for explanations and answers without a rigid agenda, where the focus is not on covering large chunks of material but on fully understanding even the smallest details. Of course, one can follow up a lecture by finding and reading the relevant published papers on the topic. However, most of the exciting findings in neuroscience are hidden in the small print of specialty journals, often written in a specialized and arcane language comprehensible to, at most, a handful of specialists. Overwhelmed with new and important discoveries in the various subsubspecialties, the practicing neuroscientist, such as myself, tends to forget that

3. The idea that the brain's main goal is to control movement has been repeatedly emphasized by several outstanding individuals. Indeed, the brain's only means of interacting with the world is via the motor system, whether foraging for food or communicating by speech, gestures, writing a paper, or sending an e-mail. The outstanding books by Gallistel (1980) and Llinás (2001) discuss this point eloquently. The "primacy" of movement has been emphasized by Hamburger et al. (1966) and Bullock and Horridge (1965). For recent reviews on this topic, I suggest Hall and Oppenheim (1987), Wolpert and Ghahramani (2000), and Robinson and Kleven (2005).

neuroscience is of startling relevance to a contemporary society wrestling with complex issues such as social behavior, depression, and brain aging. It is hard to predict which of the numerous fundamental discoveries could alter the face of such large issues, and unless they are conveyed to others, they might be overlooked without making an impact. This is mainly so because the explanations we provide in papers to the superspecialists may be impenetrable to the uninitiated. Without attempting to place our work into a larger context from time to time, we deprive ourselves of the chance to be able connect to the more macroscopic and microscopic levels of research. Yet, discoveries and insights realize their power only when understood by others. Understanding this important connection is what mostly motivated me to write this volume.

Neuroscience has provided us some astonishing breakthroughs, from noninvasive imaging of the human brain to uncovering the molecular mechanisms of some complex processes and disease states. Nevertheless, what makes the brain so special and fundamentally different from all other living tissue is its organized action in time. This temporal domain is where the importance of research on neuronal oscillators is indispensable, and it is this temporal domain that connects the work discussed in this volume to all other areas of neuroscience.

Parallel with the amazing progress in neuroscience, another discipline has emerged: complex systems, a new science that cuts across many fields. During the past decade, I have learned as much about the brain by reading about novel branches of physics, engineering, mathematics, and computer science as I did from studying papers directly dealing with the nervous tissue. Rest assured, the human brain is the most complicated machinery ever created by nature. Nevertheless, it is truly exciting looking for concepts, mechanisms, and explanations that are common among many different systems and cut across the living/nonliving dichotomy. Seemingly unlikely sources such as fractals and Internet communication have provided novel clues for understanding neuronal networks. My goal is to illustrate how this new knowledge is being incorporated into neuroscience at a breathtakingly high speed and to convey fascinating discoveries to neuroscientists, psychiatrists, neurologists, and the growing group of computational scientists, physicists, engineers, and mathematicians interested in complex systems. A covert agenda is that, along the way, describing these new discoveries will encourage outsiders to become brain rhythm enthusiasts.

Deciphering the code of the brain will have a lasting impact on our society. It is not simply an intellectual exercise for a handful of esoteric individuals anymore. It is also more than a "just" a brain-health–related issue, which affects millions in the United States and many more worldwide. As Robert Noyce, the co-inventor of the integrated circuit, once put it: "In order to understand the brain, we have used the computer as a model for it. Perhaps it is time to reverse this reasoning. To understand where we should go with the computer, we should look to the brain for some clues." Now that our economy, financial institutions, education system, research programs, distribution systems, human interactions, politics, and defense have all become computer and Internet dependent, this quest is more acute than ever. The hope is that the new knowledge about the brain will not only

inspire novel designs for computer architectures and a more efficient and safer electronic communication but also, at the same time, provide a better understanding of ourselves. Books, computers, and Internet communication have *externalized* brain functions and provided virtually unlimited storage space for the accumulated knowledge of humankind. However, this externalized information is only as useful as its accessibility. Currently existing search engines, such as Google and Yahoo, that provide access to this externalized knowledge are very inefficient (even though they are the best available at present) compared to the brain's ability to retrieve episodic information, because neuronal networks utilize fundamentally different strategies for the reconstruction of events and stories from fragments than do search engines. Understanding the brain's search strategies may allow us individuals to have better access to the cumulative knowledge of humankind.

Writing to a general audience interested in neuroscience is a much more arduous exercise than writing scientific papers. Scientists, rather than just the science they have produced, and metaphors that are deliberately absent in specialty journals come to the fore. This process inevitably implies oversimplification from the experts' viewpoint, occasional redundancies, and some rugged transitions for the novice. To alleviate the inevitable, I have written a simplified main story, which I hope to be a relatively easy read in most Cycles. Each Cycle ends with a brief summary, which highlights the primary message of the Cycle. The main story is supplemented by extensive footnotes, which serve partly to define novel terms. In most cases, however, they provide further critical information for the more sophisticated reader, along with links to the appropriate literature. I have deliberately chosen this format because it allowed me to interweave the main story and its more complex ramifications without breaking the flow of thought. The additional comments and citations in the footnotes give rise to an ever-growing tree with intertwined branches of arguments, hypotheses, and discovery.

A couple of years ago, we hosted a painter in our house for the summer. His determined goal was to survey and conquer the New York City art market. Yet, after a month or so, he plainly declared to us that every painting has already been painted and the art dealers are aware of all potential innovators in case the market is in need of such redundancy. He returned to Europe the next day. This is how I felt while writing this book. Clarity, critical details, and giving proper credit compete for space, and achieving the appropriate balance is the most difficult thing in writing a book. The more I explored the mysteries of brain oscillators and neuronal functions, the more I realized that the fundamental ideas (some which I thought were genuinely mine) have already been expressed, often repeatedly. Many times the ideas have come up in studying systems other than the brain, or they were expressed in a different context. But they existed. The deeper I ventured into the problems, the further back in time I had to travel to discover the origin of thoughts.

An oft-heard marketing slogan these days is that we have learned more about the brain during the past decade that during the previous history of humankind. This may be true regarding the volume of factual knowledge. But discoveries are

not (just) facts. They are ideas that simplify large bags of factual knowledge. Such fundamental ideas rarely pop up suddenly. Typically, they slowly emerge after appropriately long incubation periods and are shaped by numerous proponents and critics. Fundamental ideas are rare, and probably as many have been conceived prior to modern neuroscience as in the past few decades. One just has to recognize and adapt the old thoughts to the new lingo and the findings we have recently generated. My dear mentor advised me in my student days, "do not publish when you have only data but when you have a novel idea." If I followed his advice strictly, I would perhaps still be writing my first paper and this volume would not exist. Although I honestly attempted to reach a balance between summarizing large chunks of work by many, and crediting the deserved ones, I am aware that I did not always succeed. I apologize for those whose works I unintentionally ignored or missed. To claim innocence, I shall simply shift the responsibility onto those who kindly read some parts of the manuscript at various stages and did not complain (enough). These generous colleagues include Kamran Diba, Caroline Geisler , Robert L. Isaacson, Kai Kaila, Christof Koch, Nancy Kopell, Rodolfo Llinás, Stephan Marguet, Edvard Moser, Denis Paré, Marc Raichle, Wolf Singer, Anton Sirota, Paula Tallal, Jim Tepper, and Roger Traub. My dear friend Mircea Steriade took the trouble of reading the entire manuscript and provided invaluable feedback. My special thanks to Mary Lynn Gage for her attempts to transpose my Hungarian-Zombi idioms into comprehensible English. This may not have always succeeded, and I would like to publicly apologize for humiliating Shakespeare's beautiful language here and there.

At a more general level, I would like to express my gratitude to a number of people whose examples, support, and encouragement sustained me in difficult times and whose collaborations, inspiring discussions, and criticism have served as constant reminders of the wonderful collegiality of our profession—David Amaral, Per Andersen, Albert-László Barabási, Reginald Bickford, Yehezkel Ben-Ari, Anders Björklund, Brian Bland, Alex Borbely, Ted Bullock, Jan Bures, Gábor Czéh, János Czopf, Eduardo Eidelberg, Jerome (Pete) Engel, Steve Fox, Walter Freeman, Fred (Rusty) Gage, Mel Goodale, Charlie Gray, James McGaugh, Michale Fee, Tamás Freund, Helmut Haas, Michael Häusser, Walter Heiligenberg, Bob Isaacson, Michael Kahana, George Karmos, Nancy Kopell, Lóránd Kellényi, Gilles Laurent, Joe LeDoux, Stan Leung, John Lisman, Rodolfo Llinás, Nikos Logothetis, Fernando Lopes da Silva, Jeff Magee, Joe Martinez, Bruce McEwen, Bruce McNaughton, Richard Miles, István Mody, Robert Muller, John O'Keefe, Marc Raichle, Jim Ranck, Menahem Segal, Terry Sejnowski, Larry Squire, Wolf Singer, David Smith, Peter Somogyi, Mircea Steriade, Steve Strogatz, Karel Svoboda, David Tank, Jim Tepper, Alex Thomson, Giulio Tononi, Roger Traub, Cornelius (Case) Vanderwolf, Olga Vinogradova, Ken Wise, Xiao-Jing Wang, and Bob Wong. Over the years, some of these outstanding colleagues—Bob, Bruce, David, Gábor, Helmut, István, Karel, Mircea, Peter, Rodolfo, Roger, Rusty, Ted, Tamás, and Wolf—became my trusted, close friends. Most importantly, I would like to thank my students and post-doctoral fellows without whose dedication and hard work the many experiments discussed in this volume would not exist.

Being a scientist is a dedication. Writing a book is a bit more. Oh yes, it is a lot of fun, but it takes time, precious time that I had to steal from somewhere, mostly from my family. My dear wife, Veronika, and my sweet daughters, Lili and Hanna, forgive me for the many weekends you had to spend without me and for my frequent mental absences at dinners and family events when only my body was present. How fortunate I am to have you as my supporters. Without your understanding and encouragement, this venture would have been worthless.

Dear reader. Do not stop here! The rhythm begins only now.

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Cycle 1

Introduction

> There is no good reason to assume that the brain is organized in accordance with the concepts of folk psychology.
>
> —Cornelius H. Vanderwolf

It all began with a dream. A young officer in the Prussian Army received a letter from his sister. In it she wrote about a dream in which her beloved brother fell off his horse and broke his leg. As it happened, the young officer indeed fell off his horse at about the time the letter was sent by his sister. The officer, Herr Doktor Hans Berger, already an established researcher on cerebral blood circulation at the University Clinic for Psychiatry in Jena, Germany, thought that such coincidence could only have happened through some mysterious communication between brains, via telepathy,[1] as such alleged communications between brains are better known.

After returning to Jena from active military duty, Berger was promoted to the Chair of the Department of Psychiatry and Neurology in 1919 and devoted the rest of his career to the study of the brain's electrical activity. Berger reasoned that the electromagnetic forces generated by the human brain could be the carrier waves of telepathy, his true interest. Since even in that day telepathy was regarded as an "occult" subject, his experiments were conducted in utter secrecy in a laboratory located in a small building on the grounds of the clinic. Most of his initial recordings were done on himself, his son Klaus, and patients with skull defects.

1. Telepathy (or the related terms precognition and clairvoyance) is the supposed ability to transfer thoughts, feelings, desires, or images directly from the mind of one person to the mind of another by extrasensory channels and without using known physical means.

He performed numerous experiments and, importantly, eliminated the possibility that the voltage changes measured by his string galvanometer were an artifactual consequence of blood pressure changes; nor did they arise from the scalp skin. After five years of experimentation, he concluded that the most prominent electrical activity could be recorded from the occipital (lower rear) part of the skull when the subject's eyes were closed. In his groundbreaking 1929 paper he wrote, "The electroencephalogram represents a continuous curve with continuous oscillations in which . . . one can distinguish larger first order waves with an average duration of 90 milliseconds and smaller second order waves of an average duration of 35 milliseconds. The larger deflections measure at most 150 to 200 microvolts. . . ."[2] In other words, the electrical field generated by millions of discharging neurons in the cerebral cortex is 10,000 times smaller than that provided by an AA battery.

Berger called the large-amplitude rhythm (approximately 10 waves per second, or 10 hertz), which was induced by eye closure in the awake, calm subject, the "alpha" rhythm because he observed this rhythm first. He named the faster, smaller amplitude waves, present when the eyes were open, "beta" waves. Paradoxically, Berger's recordings provided firm physical evidence *against* his idea that waves generated by one brain could somehow be detected by another brain. The voltage changes that emerge from the cooperative activity of neurons in the mammalian brain are just too small, and current propagation requires a low-resistance conductor, so it cannot cross air, for example. Although he failed to prove his hypothesis of telepathic communication between brains, his research created a powerful scientific and clinical method for investigating quickly changing brain activity.[3]

Discovering a dynamic brain phenomenon is one thing. Understanding its meaning and its role in behavior and cognition is quite another. Ever since Berger's

2. Berger (1929). Berger was already familiar with the work of Richard Caton, a Liverpool surgeon who studied the electricity generated by the brains of rabbits and monkeys (Caton, 1875). Berger's international fame was boosted when his work was confirmed and endorsed in by Edgar Douglas Adrian and Bryan Harold Cabot Mathews of the Cambridge Physiological Laboratory. They suggested calling the alpha waves the Berger rhythm, but Hans Berger modestly rejected the offer (Adrian and Mathews, 1934).

3. It is tough to be first in any field of science, and the discovery of the electroencephalogram (EEG) was no different. In addition to Caton's work, Berger also knew about the published works of the physiologists Adolf Beck of Poland and Vladimir Pravdich-Neminski (or W. W. Prawdicz-Neminski in his native Ukrainian) of Russia. Neminski's observations are perhaps most relevant since his "electrocerebrogram" was obtained from the intact surface of dogs' skulls (Neminski 1913). However, he was not the first Russian in this area of research. Vasili Yakovlevich Danilevsky had described observations similar to Caton's in his doctoral thesis, and Nikolai Y. Wedensky had used a telephone circuit to listen to electrical waves in the brains of cats and dogs. Fleischel von Marxow was also among the first discoverers of electrical fields of the brain. However, he placed his results in a sealed letter in 1883 and revealed them only after he learned about Beck's published results. What made Berger's observations stand out from the others were the numerous control experiments he provided along with his observations. Brazier's (1959) chapter is the best summary of the exciting early days in the study of brain electricity and is a source for numerous references. Borck (2005) is another useful source of historical materials.

early observations, three questions have haunted neuroscientists: how are EEG patterns generated, why are they oscillatory, and what is their content? Providing answers to these questions is a major goal of this volume. I introduce the topic in Cycles 2 and 3 by discussing the important issue of how the speed of communication in the cerebral cortex can be preserved despite the great size differences of the brains of small and large mammals. Cycle 4 can be skipped by those who have had an introductory class on methods in neurophysiology. It discusses the major methods currently available for investigating brain activity patterns in living tissue and the mechanisms that give rise to the field EEG. Cycles 5 and 6 serve as an introduction to the different types of oscillators and discuss the large family of oscillations in the mammalian cortex. Cycles 7 and 8 are devoted to the "default" states of the brain: sleep and early brain development. Tying the macroscopic features of oscillations to neuronal mechanisms requires large-scale recordings of numerous single neurons. Such techniques allow us to gain some insight into the content of oscillations, which is described in Cycles 9–12. In Cycle 13 I examine the structural and functional requirements of awareness by contrasting brain structures that can and cannot support self-generated patterns and long-range communication through global oscillations.

Periodic Phenomena in Nature

Nature is both periodic and perpetual. One of the most basic laws of the universe is the law of periodicity.[4] This law governs all manifestations of living and nonliving. In its broadest definition, periodicity refers to the quality, state, or fact of being regularly recurrent: a repeating pattern or structure in time or space. What goes up must come down. The sun rises and sets, and the days wax and wane. Without periodicity, there is no time; without time, there is no past, present, or future. In living systems, the periodicity of individual lives gives rise to the continuity of life on Earth. Our existence has meaning only when experienced in time. The essence of music and dancing is rhythm. An important part of human culture is the celebration of the periodicity of life. The Jewish and Muslim religions are attuned to the lunar cycle. Christians adopted a solar calendar. Periodicity can be seen in the monthly windows of opportunity for conception of human life.

Periodicity, oscillation, rhythm (from Latin meaning to flow), and cyclic process are synonyms that refer to the same physical phenomenon. Historically, different academic disciplines have adopted a preferred term to describe these related phenomena. Periodicity is the term of choice in social and earth sciences. Oscillation is the preferred term in physics, and engineers talk about cyclic or period generators. Until recently, neurologists and neuroscientists used the term "brain rhythms" almost exclusively when referring to the various brain patterns.

4. Nature, of course, has no laws, desires, goals, or drives. It simply generates certain regularities that we conveniently assume are governed by some outside forces and use a third-person perspective to refer to these regularities.

Reference to oscillations is quite recent.[5] The avoidance of the term "oscillator" in brain research for so long perhaps reflected the tacit view that brain rhythms may be qualitatively different from the oscillators discussed in physics textbooks. Assuredly, neuronal oscillators are quite complex. Nevertheless, the principles that govern their operation are not fundamentally different from those of oscillators in other physical systems. Today, it is widely recognized that the brain's ability to generate and sense temporal information is a prerequisite for both action and cognition. This temporal information is embedded in oscillations that exist at many different time scales. Our creativity, mental experiences and motor performance are modulated periodically both at short and long time scales. But how are oscillatory states brought about, especially if they occur in the absence of external influences? In Cycles 5 and 6 I propose some answers with illustrations from physics and engineering.

Time and Periodicity

Neuroscientists work with time every day but rarely ask what it is. We take for granted that time is "real" and that brains have mechanisms for tracking it. Since time is a major concept in this book, I attempt to provide a working definition without getting lost at the nebulous boundary between physics and philosophy.[6] Newton held that time flows in absolute intervals, independent of the physical universe. According to Immanuel Kant, space and time are irreducible categories through which reality is perceived by our brains. Albert Einstein combined space and time into "spacetime." According to him, time is a measure of motion and, as such, is part of the physical universe and thus could be interpreted as its "property"; space and time disappear along with the things. An opposite view is that time is a subjective abstraction and does not exist in any physical substrate and has no more reality than a mathematical axiom. In a broad sense, time is a *measure of change,* a metric of succession, a parameter that distinguishes separate events. One practical definition is that "time is that which is measured by a clock," a pragmatic description adequate for most branches of physics and neuroscience.[7]

How we approach the problem of time largely determines our view of the outside world around us. First, we need to distinguish two aspects of time. Absolute time is clock time, referring to a particular point in a time series, for example, your birth date. Absolute time is a fundamental element of existence since everything

5. It was the review by Steriade and Deschênes (1984) that popularized the term "neuronal oscillator" in the mammalian nervous system. See also Steriade and Llinás (1988).

6. Hawking (1992) is an excellent introduction to this difficult topic. Hall (1983) is another easy read. A radically different definition of time is proposed by Leyton (1999). Leyton derives time from spatial symmetry and its broken version: time is essentially symmetry breaking (e.g., asymmetric representation of plane symmetry by oscillatory phase; see Cycle 11).

7. In physics, standard time interval (a second) is defined by an oscillator: 9,192,631,770 hyperfine transitions in the ^{133}Cs atom.

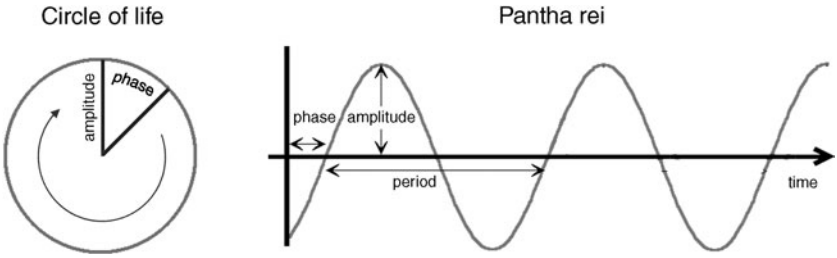


Figure 1.1. Oscillations illustrate the orthogonal relationship between frequency and time and space and time. An event can repeat over and over, giving the impression of no change (e.g., circle of life). Alternatively, the event evolves over time (*pantha rei*). The forward order of succession is a main argument for causality. One period (right) corresponds to the perimeter of the circle (left).

exists in time. Duration refers to the change of time, the interval between two points in time. Elapsed time is therefore relative, and it has an interval span (e.g., hour), whereas absolute time does not have a span (e.g., date). We make a similar absolute versus relative distinction in space as well, when we talk about position and distance. However, while distance can refer to many directions (vector) in space, time has only one direction (scalar).

The intimate relationship between space and time is packaged into the concept of "spacetime" (x, y, z, t dimensions). Oscillations can be conceived of and displayed in terms of either space or time. The phase-plane of a sinusoid harmonic oscillator[8] is a circle. We can walk the perimeter of the circle once, twice, or billion of times and yet we always get back to our starting point. "What has been is what will be, and what has been done is what will be done; and there is nothing new under the sun"[9] This is the "circle of life," and our walk on its perimeter is measured as dislocation (figure 1.1, left).

An alternative to the periodicity view of the universe is to display periodicity as a series of sine waves. Now we can walk along the troughs and peaks of the line without ever returning to the starting point (figure 1.1, right). Time here is a continuum with the cycle as its metric. The cycles are identical in shape, and the start and end points of the cycles form an infinite path into the seemingly endless universe. This meandering line illustrates the basis of our time concept: *linear*

8. The different types of oscillators are defined and discussed in Cycle 6.

9. The quote is from the book of Ecclesiastes (chapter 1, verse 9, Revised Standard Version). The concept of recurrence is prominent in Hinduism and Buddhism, among others. The spoked wheel of life (*dharma*) is an endless cycle of birth, life, and death. The concept of recurrence is also prominent in Friedrich Nietzsche's philosophy (best expressed in *Also Sprach Zarathustra. Ein Buch für Alle und Keinen*). A picture of nature as being in "balance" often prevails in both biological and religious discussions. Although a general equilibrium theory has never been explicitly formulated, environmentalists and conservationists tacitly assume that nature is in an eternally stable equilibrium; therefore, we should keep it that way. However, if this were the case, how did we get here in the first place?

change and a *forward order* of succession, features that are often used in arguments of causality. A moment never repeats itself. *Pantha rei*—everything flows—according to the ancient Greek saying. "Upon those who step into the same rivers, different and ever different waters flow down."[10] Whichever model we choose, the circle or the meandering line, in periodically changing systems the past can predict the future (position or moment).

The hard problem to solve is whether time and space are situated in our minds only or whether they in fact exist independently of us. Fortunately, most brain operations, including predictions by brain rhythms, can be understood without addressing this hard problem. Clock time is sometimes referred to as objective time, an absolute physical reality, independent of conscious brains and beyond our control. Clock time is what we use to calibrate our subjective experience of the passage of time and coordinate our thoughts and activities. Passage of time, that is, its duration, is felt as a linear event, slipping from one moment to another. The *feeling* of time is confined to a relatively short span from tens of milliseconds to tens of minutes. As shown in Cycle 5, this time span corresponds to the temporal range of brain oscillators, which may serve as an internal metric for time calibration. Nobody can feel micro- and nanoseconds, and tracking time durations beyond the hour range requires body references such as hunger or feedback from the environment. Our best temporal resolution is in the subsecond range, corresponding to the duration of our typical motor actions, the tempo of music and speech.[11]

Linear time is a major feature of our Western cultural world-view, and the experience of time flowing between past, present, and future is intricately tied to everyday logic, predictions, and linear causation. According to the great French molecular biologist Francois Jacob, "one of the deepest, one of the most general functions of living organisms is to look ahead, to produce future."[12] What I am proposing in this volume is that neuronal oscillations are essential for these deepest and most general functions.

Time, Prediction, and Causation

Causality among world events is linked to our perception of time.[13] Prediction, inference, forecast, and deduction are used as synonyms in the context of proposed

10. The quote is attributed to Heracleitus of Ephesus (540 to circa 475 B.C.).

11. The average duration of syllables, the fundamental segmentation of speech in all languages, is approximately 250 milliseconds. Syllables cannot be stretched or sped up at will in spoken language beyond certain limits. Slowing down speech can be achieved only by introducing long pauses between syllables. This is the reason why it is so difficult to understand the text of arias.

12. Jacob (1994), p. 32.

13. Freeman (2000) explains that time exists in the material world but causality does not. Along with physicists, he argues that time is a measure of motion, living and nonliving; therefore, it is an objective dimension. In contrast, cause is a measure of intent, and, according to Freeman, only humans have intent.

causality. They refer to an inductive process, which integrates information about the past and present to calculate the following most probable outcome.[14] Brains help their owners to survive and prosper by predicting and deciphering events in the world, including consequences of their own actions. Predictions and relationships are constructed by ordering the succession of events according to elapsed subjective time. We are usually able to say which of two events happened before the other, with decreasing precision as time elapses. Causal-explanatory relationships are usually considered a one-way process because such relationships are embedded in the context of time and time is asymmetric and unidimensional. The cause precedes the effect in time. If the discharge of neuron *a* consistently and reliably precedes the discharge of neuron *b,* and after destruction of neuron *a* neuron *b* ceases to discharge, a causal relationship is suspected. Linear causation works most of the time, and it is the foundation of many essential operations from catching a ball to solving a mysterious murder case. Causation can also fail. For example, in an oscillatory system, most or all neurons with reciprocal, one-way connections or no direct connections may discharge with a zero time lag (i.e., simultaneously), making linear causation impossible, as illustrated in several subsequent Cycles. Oftentimes, the reason for causation failing can be explained by the discrepancy between objective or external time and subjective time registered by the brain.

According to the second law of Newtonian mechanics, a body tends to remain in its state of rest or motion unless acted upon by an external force.[15] The force is the cause, an agent responsible for the motion of the body. When a moving billiard ball hits a stationary one, the latter begins to move. This happens because the kinetic energy of the moving ball exerts force on the stationary ball, causing it to move. Now consider the following psychophysical experiment. A ball is moving toward another one, this time not on a pool table but on a computer screen. If the second ball starts moving in the same direction after the arrival of the first ball, we conclude from the timing of the events that the first ball caused the second one to move. However, derivation of such a conclusion depends critically on the exact timing of the events. We make the inference of causality only if the second ball begins to move within 70 milliseconds after the first ball reaches it. If at least 140 milliseconds elapse between the halting of the first ball and movement of the second ball, no causality is suspected. Between 70 and 140 milliseconds of delay, the two disks appear to stick together but some indirect causality is still deducted.[16] Thus, temporal context is critical for

14. The most influential theory on prediction was put forward by Thomas Bayes (1763/1958). His probability theory examines the possible outcomes of events in terms of their relative likelihoods and distributions (Bernardo and Smith 1994). A "brain computation-relevant" treatment of the Bayesian theory is discussed by Changizi (2003).

15. The second law also nicely illustrates the reductionistic nature of prediction: knowing all past (upstream) events, the future probabilities can be calculated; no goals, desires, or teleology is involved.

16. This is a classic experiment by Shallice (1964). See related arguments in Eagleman and Sejnowski (2000) and VanRullen and Koch (2003).

perception, including the perception of causation. The brain "chunks" or segregates perceived events according to its ability to package information in time, and such packaging, I propose, can be achieved by neuronal oscillators (Cycles 9 and 11).

Here is another illustration of a "logical illusion" in which the brain falsely reconstructs the order of events. You are driving on a highway and a deer crosses the road. You slam on the brakes and avoid a collision. The mental reconstruction of the events is as follows. You noticed a deer (cause) and realized that it would be dangerous to hit the animal. So you decide to avoid it, push the brakes, and turn the steering wheel (effects). Laboratory replication of such real-world actions offers a different explanation. A deer appeared (first event), you braked (second event), and *then* you recognize the animal (third event). This sequence is proposed because reaction time to an unexpected event is less than half a second, whereas conscious recognition requires the recruitment of a large number of neurons in a large, distributed complex brain circuit, which takes longer than half a second.[17] The false logic emerges from the difference between external time and brain-reconstructed time.

Although in this case a simple cause–effect (unexpected object–braking) relationship exists, mental reconstruction offers a different cause. The brain takes into consideration the conduction velocities of its own hardware and compensates for it. For example, touching your nose and toe at the same physical time (or touching your nose with your toe) feels simultaneous even though neuronal events in the cerebrum, representing the touch of two body parts, are delayed by several tens of milliseconds. The conclusion that follows from this discussion is that our time reconstruction is a consequence of an accumulation of past experience rather than a truthful representation of real time. Nevertheless, despite the difficulty in deducting causality, the above examples are simple because they involve a single well-defined cause. In many cases, the causes are multiple and so pointing to a single cause or agent is not possible. Deducing causality is particularly difficult when the cause involves a reciprocal relationship between parts and wholes, as is often the case for neuronal oscillations and other properties of complex systems.

Self-Organization Is a Fundamental Brain Operation

The brain is perpetually active, even in the absence of environmental and body-derived stimuli. In fact, a main argument put forward in this book is that most of the brain's activity is generated from within, and perturbation of this default pattern

17. Libet (2004) gives an extensive analysis of "mind time," a neuronal process evolving over time, needed for conscious experience (see also Libet, 1973). Other experiments show that events registered by the brain shortly after the stimulus (<100 milliseconds) may be used to update motor programs even though the person does not subjectively experience them (Goodale et al., 1986).

by external inputs at any given time often causes only a minor departure from its robust, internally controlled program.[18] Yet, these perturbations are absolutely essential for adapting the brain's internal operations to perform useful computations. Without adjusting internal connectivity and computations to the spatial and temporal metrics of the external world, no constructive, "real-world" functions can be generated by the brain.[19] In engineering terms, this process can be referred to as "calibration." The self-reliance of brain circuits increases as we move to higher levels in the brain, ones that have less and less contact with sensory inputs.

Due to its ability to give rise to spontaneous activity, the brain does not simply process information but also *generates* information. As a result, the world outside is not simply "coded" by meaningless "bits" of neuronal spikes but gets embedded into a context, an important part of which is time. "Representation" of external reality is therefore a continual adjustment of the brain's self-generated patterns by outside influences, a process called "experience" by psychologists. From the above perspective, therefore, the engineering term "calibration" is synonymous with "experience."

Paradoxically, such a view is quite recent in neuroscience research and is, of course, hard to defend if one subscribes to Aristotle's thesis that nothing moves or changes itself. The novel idea of a "self-cause"–governed principle has emerged in several disciplines and is referred to by numerous synonyms, such as spontaneous, endogenous, autogenous, autochthonous, autopoietic, autocatakinetic, self-organized, self-generated, self-assembled, and emergent. Systems with such features are often called complex.[20] The term "complex" does not simply mean complicated but implies a nonlinear relationship between constituent components, history dependence, fuzzy boundaries, and the presence of amplifying–damping feedback loops. As a result, very small perturbations can cause large effects or no effect at all. Systems in balance are simple and hard to perturb. Complex systems are open, and information can be constantly exchanged across boundaries. Despite the appearance of tranquility and stability over long periods, perpetual change is a defining feature of complex systems. Oftentimes, not only does complexity characterize the system as a whole, but also its constituents (e.g., neurons) are complex adaptive systems themselves, forming hierarchies at multiple levels. All these features are present in the brain's dynamics because the brain is also a complex system.

18. Similar views have been repeatedly expressed by both philosophers and neuroscientists. Perhaps the most explicit discussion on this issue is a comprehensive review by Llinás and Paré (1991). However, I do not believe that any useful function would spontaneously emerge in an isolated brain. As discussed in Cycle 8, environmental inputs are an absolute requirement for creating useful brain activity.

19. It is not always easy to distinguish between "internal" and "external" operators. The brain, the body, and the environment form a highly coupled dynamical system. They are mutually embedded rather than internally and externally located with respect to one another. This embeddedness must have a profound influence on all aspects of brain activity (Chiel and Beer, 1997).

20. An excellent introductory book on self-organization is Kampis (1991). The primary reference on autopoiesis and autopoietic theory, with reference to the brain, is Maturana and Varela (1980).

Ever since electrical activity has been recorded in the brain without evidence of an inducing external agent, it has been referred to as "spontaneous." Spontaneous activity has proven to be a difficult concept to tackle because the system that generates it appears to act independently of outside influences, as if there were an element of choice, directed goal, intention, or free will. Although the observation of spontaneous brain activity, in principle, offers a substitute for Thomas Aquinas's philosophical freedom of the self, two major obstacles have remained.[21] First, spontaneous activity is present in all brains, not only those of humans, yet, according to Aquinas, only humans can choose between good and bad. Second, the largest amplitude and most regular spontaneous oscillations in the cerebral cortex occur at the "wrong" time, that is, during sleep or when the brain is otherwise disengaged from the environment and body. In contrast, when decisions are made by the human subject, brain activity often does not show large-amplitude rhythms but instead appears "desynchronized" or "flat" in conventional scalp recordings.[22] As a result of these considerations, neurophysiologists downgraded the significance of spontaneous brain activity to "noise" and "idling." Ironically, although the term "self-organization" was introduced by the British psychiatrist W. Ross Ashby,[23] genuine interest in spontaneous brain activity was kindled by research and thinking that occurred in disciplines other than neuroscience.

Emergence, Self-Causation, and Adaptation

The fundamental assumption of classical thermodynamics is destruction of structure, an inevitable temporal progression from organized to disorganized, characterized by the monotonic increase of entropy.[24] In the framework of classical physics, order in nature must be created through external forces. When designing a car, many rational considerations, such as power, size, appearance, cost, and other *goals,* are first evaluated. Prior to the car's physical existence, its designers can envision many of its characteristics. Such top-down effort requires an extraordinary a priori knowledge of math, physics, engineering, computer graphics, esthetics, marketing, and other complicated stuff. Can order as complex as the brain's emerge without a "designer" and explicit goals?

While nothing contradicts the second law of thermodynamics within the realm of stable, closed systems, things are different in open, complex systems that exist

21. For a concise exposition of Aquinas's account of free choice, read MacDonald (1998).

22. In later Cycles I show that the waking brain is rich in rhythms. The "flat" EEG is most often composed of fast, low-amplitude gamma oscillations.

23. Ashby (1947). Implicitly, the idea of increasing order in nature can be traced back to Charles Darwin, but the explicit concept of self-organization matured within physics.

24. The concepts of entropy and information are deeply related. Schrödinger's negentropy (negative entropy) "is identical to information" declared Szilárd (1929/1990). In information theory, entropy reflects the amount of randomness in the signal (Shannon, 1948).

far from a state of equilibrium. In complex systems, the direction is typically from disorganized to better organized, according to physicists. Indeed, extremely complicated protein structures with multiple uses can be built by following stunningly simple algorithmic steps dictated by the variation of just four nucleic acids that form DNA. Could the "smartness" of brain organization and performance be traced back to similarly simple algorithms? Cycles 5–8 discuss arguments in favor of such "minimalism."

The new story in physics begins with the postulate of open systems, which operate far from thermodynamic equilibrium, so that the system can exchange energy, matter, or entropy with its environment. Typical examples include avalanches, earthquakes, galaxies, and, in fact, the evolution of the whole universe. The Belgian-American chemist Ilya Prigogine introduced the term "dissipative structures," which refers to patterns that self-organize in far-from-equilibrium states. The expression "far from equilibrium" means that the system cannot be described by standard linear mathematical methods. Characterization of dissipative systems requires nonlinear differential equations because there are no universal solutions. These complex systems live by the rules of nonlinear dynamics, better known as chaos theory.[25] The immediate link between problems of neuronal communication and dynamical theory is that both are concerned with the fundamental aspects of change and the time context within which the change occurs. In complex systems, the evolution of the system is described as a motion vector in a multidimensional space. The sequentially visited points in the multidimensional state space are called a "trajectory." Applying this idea, for example, to visual perception, the trajectory corresponds to the ordered assemblies of neurons set into motion, from the retina to higher visual and memory systems. The spatiotemporal trajectory of neuronal activity depends not only on the constellation of light impinging on the retina but also on the perceiver's brain state and past experience with similar physical inputs. Hence, each time the same stimulus is presented, it generates a somewhat different and unique trajectory in the neuronal space.

Complexity can be formally defined as nonlinearity, and from nonlinear equations, unexpected solutions emerge. This is because the complex behavior of a dynamic system cannot easily be predicted or deduced from the behavior of individual lower level entities. The outcome is not simply caused by the summation of some agents. The emergent order and structure arise from the manifold interactions of the numerous constituents. At the same time, the emergent self-organized dynamic, for example, a rhythm, imposes contextual constraints on its constituents, thereby restricting their degrees of freedom. Because the constituents

25. Mathematically, chaos is defined as the exponentially sensitive dependence of a system on its initial conditions, implying that there is a fundamental limit on the predictability of the system. The predictability of the system (or the lack of it) is quantified by the entropy, reflecting the rate at which past history is lost. It is equal to the sum of all positive Lyapunov exponents. The positive value of the Lyapunov exponent is the proof for the chaotic behavior of the system. A concise and excellent introduction of nonlinear dynamics to neurobiology is Freeman (1992). For more in-depth treatment, consult Prigogine and Stengers (1984), Glass and Mackey (1988), or James Gleick's bestseller on chaos (Gleick, 1987).

are interdependent at many levels, the evolution of complex systems is not predictable by the sum of local interactions. The whole is based upon cooperation and competition among its parts, and in the process certain constituents gain dominance over the others. This dominance, or *attractor* property, as it is called in chaos theory, can affect other constituents such that the degrees of freedom in the system decrease. Such compression of the degrees of freedom of a complex system, that is, the increase of its entropy, can be expressed as a collective variable. These ideas have a profound effect on the interpretation of spontaneously organized brain patterns (as discussed in Cycles 5–7).

Hermann Haken, a German laser physicist, refers to the relationship between the elements and the collective variable as synergy (he also calls it the "order parameter"), the simultaneous action of emergence and downward causation. In Haken's system of synergetics, emergence through self-organization has two directions. The upward direction is the local-to-global causation, through which novel dynamics emerge. The downward direction is a global-to-local determination, whereby a global order parameter "enslaves" the constituents and effectively governs local interactions. There is no supervisor or agent that causes order; the system is self-organized. The spooky thing here, of course, is that while the parts do cause the behavior of the whole, the behavior of the whole also constrains the behavior of its parts according to a majority rule; it is a case of circular causation. Crucially, the cause is not one or the other but is embedded in the configuration of relations. In fact, Haken argues that in synergetic systems the cause is always circular. Perhaps a better term would be "nonsymmetrical reciprocal causality."[26]

Putting the philosophical issues aside for a moment, nonlinear dynamics brought with it a novel kind of thinking about systems—not as mere aggregates of parts but as a bidirectional interaction between parts and the whole.[27] Systems that can be perturbed from outside and incorporate external influences in their future behavior possess a remarkable capacity for learning and growth even though they live within boundaries defined by simple rules. By adhering to these low-level rules, something greater than the sum of parts can emerge. The emergent level is thus qualitatively different from the level it springs from. If the component relationships within the system become optimized for a particular task as a

26. Haken (1984). Circular causation is an argument for causes directed both up and down. It is neither paradoxical nor vicious. Democratic election of a governing body (the "order parameter") guarantees the majority rule ("enslavement" of the minority). The best exposure to the role of circular causality in neuroscience is gained from Kelso (1995), an abbreviated version of which is Bressler and Kelso (2001). Freeman (1999) goes even further and describes consciousness as an order parameter, "a state variable-operator" (p. 12) in the brain that mediates the relations among neurons and, therefore, must play a crucial role in intentional behavior.

27. General system theory was first articulated by the biologist Ludwig von Bertalanffy (1968) as a response to the one-way, mechanistic cause–effect approach in living systems, including brain research. His main claim was that living things do not exist in isolation but are embedded in an orderly environment, and it is the interaction between the context and the organism that generates novel properties. A system's organization is determined primarily by the predictable relations among its constituents (e.g., synaptic connections) but can also be influenced by the components' properties (e.g., intrinsic features of neurons).

result of external perturbations, the system is called adaptive. The brain is such an adaptive complex system.[28]

Today's systems neuroscience is an offspring of general systems theory, a sort of modernized Gestalt concept in a quantitative disguise. Instead of looking at discrete moments in time, the systems methodology allows us to see change as a continuous process, embedded in a temporal context. Systems thinking and especially explorations in chaos have quickly identified an important application in neuroscience by investigating the bioelectrical activity in the brain and have claimed (premature) victory by stating that brain activity, and at times behavior, reflects chaos. How does this claim relate to our introductory discussion that the brain operates in an oscillatory mode, whose main task is prediction? Cycle 5 covers this important topic, followed by further discussion in subsequent Cycles about the relationship between the internal complexity of neuronal networks and the reliable predictions they can make about events external to the brain.

Where Does the Brain's Smartness Come From?

Even though spontaneous brain activity emerges without an external force, for a brain to be useful it should adapt to the outside world. The brain has to be calibrated to the metrics of the environment it lives in, and its internal connections should be modified accordingly. If the statistical features of the environment reflect one particular constellation, the evolving brain should be able to adapt its internal structure so that its dynamics can predict most effectively the consequences of the external perturbation forces. A great deal of this adaptive modification for each individual brain (i.e., its "smartness") comes from interactions with conspecifics, that is, other brains. In other words, the functional connectivity of the brain and the algorithms generated by such continuous modifications are derived from interactions with the body, the physical environment, and to a great extent, other beings.

One can ask a similar question at the single-component level of the brain, as well: how smart is a neuron? The answer depends on the baseline of the comparison and on the size of the brain the neuron is embedded in, because smartness is a relative judgment. In a very small neuronal network, each neuron is critical, and discernible functions can be assigned to each. In larger brains, the complexity of single neurons tends to be underestimated largely because the relative contribution of a single cell to the complex operation of the network appears small. The ratio of individual and collective "intelligence" decreases radically as the brain size grows. But it is not simply the number of neurons that matters. Instead, it is the connectivity and the connectivity-confined communication that largely determines the share single neurons have in brain computations.

28. "Adaptation," of course, inevitably invokes the philosophically charged terms "goal directedness" and teleology. Here the causes are backward in time because actions are guided by downstream goals, motivational targets, or desires (Edelman 1987).

It is much like the smartness issue with us humans. Prior to our cultural evolution, as is the case in other animals, there was not much difference between individual and species knowledge. However, with the invention of books, computers, and the Internet, an ever-increasing portion of knowledge has become externalized from individual brains. As a result, the primary carrier of species knowledge is no longer the individual or the collective wisdom of tribe elders (i.e., their brains). Because of technology-enhanced externalization of information, the cumulative knowledge of humankind is constantly growing, whereas the *relative* share of the average individual, sadly enough, is steadily decreasing. Similarly, the relative smartness of individual neurons decreases with brain growth, despite their preserved or even improved biophysical properties. The reason is that single neurons develop their smartness through their interactions with local peers. With growing brain size, single cells get less and less informed about system level and global decisions. In a strongly interconnected system, such as the mammalian cerebral cortex, changes in a single neuron or neuronal assembly can ripple throughout the entire cortex. However, the impact of the distant effects decreases rapidly as brain size grows due to the expense of maintaining distant connections. The selective and specific response of a single cell, that is, the degree of its "explicit" representation, is not a function of its biophysical or morphological properties but depends largely on its functional connectivity in the network. Thus, there are no smart neurons; their explicitness derives simply from being at the right place at the right time. A special challenge, therefore, is to explain how brain complexity scales with the size of growing networks while still preserving the useful functions of simpler brains. Cycles 2 and 3 dealing with the anatomical architecture of the brain and Cycles 5–11 addressing the statistical features of its global activity attempt to illuminate these issues.

Causation and Deduction

An objection can be raised that the entire project of "dynamical systems" is guilty of vicious circularity. It just explains away the real problem, the cause–effect relationship. Self-emergence of spontaneous activity is indeed a difficult conception because there is always an element of a "goal" or "will." One can adopt the practical view that this implication is primarily verbal rather than philosophical and perhaps need not be taken very seriously. Nevertheless, everyday experience dictates that logic should follow the path of linear causation and avoid circularity. But linear causation is not foolproof, either, as is amply illustrated by the fundamental deductive error made by the great master of logic himself, Aristotle. He flatly denied that the brain has anything to do with cognitive and motor functions: "The seat of the soul and the control of voluntary movement—in fact of nervous functions in general—are to be sought in the

heart. The brain is an organ of minor importance, perhaps necessary to cool the blood." This declaration was a major attack on the correct view, expressed almost a century earlier by Hippocrates: "Men ought to know that from the brain and from the brain only arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, we think, see, hear and distinguish the ugly from the good, the pleasant from the unpleasant. . . . To consciousness the brain is messenger."[29] Aristotle's linear causation managed to suppress the correct view for more than a millennium. His revisions were based on several *deductive* arguments. The heart is affected by emotion (the brain does not react). All animals have a heart, and blood is necessary for sensation (he thought the brain was bloodless). The heart is warm (he thought the brain was cold). The heart communicates with all parts of the body (he was ignorant of the cranial nerves). The heart is essential for life (the brain is not essential, he thought). The heart is the first organ to start working and last to stop (the brain develops later—this is somewhat true). The heart is sensitive (the brain is not). The heart is in the middle of the body and is well protected (the brain is exposed). However, Aristotle was not unique in his views. The kings of Egypt were prepared for the afterlife with virtually all body parts preserved, but the brain was scooped out and tossed away. The Bible never mentions the brain and relates emotional and moral behaviors foremost to the heart, the bowels, and the kidneys. Interestingly, similar ideas about the importance of various organs occurred in other cultures, as well. According to the Talmud, one kidney prompts man to do good, and the other to do evil. "We red men think with the heart," claimed the Pueblo Indians.[30]

How can we argue against overwhelming intuitive "evidence," such as the "logical" examples cited above?[31] Surely facts are needed, but facts are always interpreted in context. Is the proper context linear time, brain-reconstructed time, or something else? Of course, similar skepticism can be expressed within the framework of dynamic complex systems. What does it mean to conjecture that the brain is a pattern-forming, self-organized, nonequilibrium system governed by nonlinear dynamical laws, and how should we prove or disprove this? The intuitively simple concept of self-organization or spontaneous activity has proven notoriously difficult to pin down formally.[32] It has remained a challenging task for systems neuroscience to go beyond the most general types of explanations and elucidate the brain-specific mechanisms. General systems theory and nonlinear

29. The quote from Aristotle is cited in Nussbaum (1986; p. 233). The quote from Hippocrates is cited from Jones (1923, p. 331), Hippocrates (400 B.C.).

30. For further readings on the topic, I recommend Changeux (1985) and Vanderwolf (2003).

31. Marvin Minsky's oft-cited quote "Logic does not apply to the real world" illustrates the paradox of Aristotelian logic and causation.

32. Several prophetic manifestos have been attempted in this direction (Walter, 1952; Amari, 1982; Freeman, 1991, 1992; Haken, 1984; McKenna et., 1994; Kelso, 1995). However, a substantive experimental research effort is needed for real progress on the complexity problems of the brain.

dynamics have provided useful concepts and novel paths for thinking, but the mechanism-level research is left for neuroscience.[33]

Adopting the systems view poses difficulties for an experimentalist; it is already a daunting task to understand the neurons and neural circuits in isolation. Examining the relationship between the collective-order parameters and activity of individual neurons in sufficiently large numbers, and taking into account their past patterns—and doing it all at the same time—make the problem even harder. Nevertheless, spectacular progress has been made on this front, which is reported in Cycles 9–12. Unfortunately, it is not always practical to attempt to monitor and interpret everything at once. Even if we are aware that interactions at multiple levels subserve a physiological function, oftentimes progress can be made only after simplifying either the hardware (by looking at small pieces of the brain) or the operations (by anesthetizing the brain or keeping its environment constant). The paramount importance of nonlinear dynamics notwithstanding, it is fair to say that, to date, most of what we know about the brain in general, and about its physiological operation in particular, has been discovered using simplified preparations and linear methods. Not surprisingly, the relationship between the parts and the whole has been a much-debated topic in neuroscience, as well. Because most studies in the past were carried out within either a top-down or bottom-up framework, we should first examine the merits of these approaches before declaring them obsolete.

Scientific Vocabulary and the Direction of Logic

The ever-traveling great mathematician Paul Erdös fantasized that God was an architect. Erdös contended that the architectural plan of God's creation is detailed in a hidden "Book," whose teachings we have to discover using mathematics. Every single problem mathematicians would ever encounter is detailed in the "Book." Thus, according to Erdös, and mathematicians siding with him, the science of mathematics is not a human-invented universe of axiom-based relationships but a "reality" that exists a priori and is independent of mathematicians.[34] We just have to discover this reality. The alternative view, of course, is that math

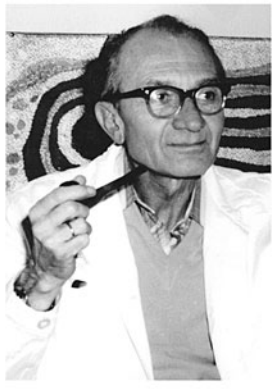
33. It is important to distinguish between concepts and mechanisms. Concepts are substrate independent, whereas particular mechanisms always depend on some kind of a substrate. Although concepts borrowed from other disciplines can assist in addressing a problem or gaining a new insight, understanding mechanisms always requires experiments on the relevant substrate (the brain, in our case). Concepts can be developed by introspection, but their validity can be confirmed or rejected only by confronting them with mechanisms. A general problem in neuroscience is that the same terms are often used interchangeably as concepts or mechanisms (e.g., inhibition of memory as a concept and inhibition as a mechanism).

34. According to one of his students, János Komlós (personal communication), Erdös was not happy with just any solution, and he did realize that there might be multiple solutions to the same problems, just as a multitude of models can mimic various brain functions. Erdös believed that only one, the simplest and most elegant, solution for each problem was in the "Book."

is simply invented by the human mind. We may ask a similar question within the framework of neuroscience. Are our top-down concepts, such as thinking, consciousness, motivation, emotions, and similar terms, "real," and therefore can be mapped onto corresponding brain mechanisms with similar boundaries as in our language? Alternatively, do brain mechanisms generate relationships and qualities different from these terms, which could be described properly only with new words whose meanings have yet to be determined? Only the latter approach can address the issue of whether the existing concepts are just introspective inventions of philosophers and psychologists without any expected ties with brain mechanisms. I believe that the issue of discovery versus invention is important enough to merit illustration with a piece of neuroscience history.

If brain rhythms are important order parameters of large-scale neuronal behavior, it is tempting to relate them to cognitive processes. The first rhythm that acquired this distinguished role was the hippocampal "theta" oscillation (4–10 hertz in rodents). This large-amplitude, prominent rhythm was first described in the rabbit under anesthesia, but it became the focus of attention only after Endre Grastyán demonstrated a relationship between theta oscillation and the orienting reflex in behaving cats. His finding marked the beginning of five decades of search for the correct term that unequivocally describes the behavioral correlate of theta oscillations. By the time I became a postdoctoral fellow in Cornelius (Case) Vanderwolf 's laboratory at the University of Western Ontario, Canada, in 1981, virtually every conceivable overt and covert behavior had been advocated as the *best* behavioral correlate, often followed by passionate debates among the contenders. Following Grastyán's pioneering work, many related terms and concepts, such as attention, selective attention, arousal, information processing, visual search, and decision making, have been added to the ever-growing list. All these studies shared the view that the hippocampal theta oscillation is associated with some high-level processing of environmental inputs. At the other extreme of the list were hypotheses suggesting an "output" or motor control role of hippocampal theta. The most influential of these hypotheses has been the "voluntary movement" hypothesis of Vanderwolf. His contention was that theta oscillations occur during intentional or voluntary movement, as opposed to immobility and "involuntary" movement, that is, stereotypic activity.[35] The many postulated functions of theta, across the spectrum from processing to production, included some exotic functions, such as hypnosis, brain pulsation, temperature change, and sexual behavior or, more precisely, mounting and copulation (figure 1.2). My best hope of a claim to fame as a postdoctoral fellow seemed coming up with yet another term that would be distinct from all the previous ones while remaining compatible in spirit to those introduced by my graduate and postdoctoral mentors.

35. Vanderwolf (1969, 1988). The neurosurgeon John Hughlings Jackson distinguished voluntary and automatic-reflexive movements. Voluntary is supposed to have a fully internal cause. For Plato and St. Augustine, voluntary behavior is free in the sense of being totally unrelated to anything in the external world. One can argue, however, that even the free choice of desire can be activated by external objects, since the brain is embedded in the body–environmental context.



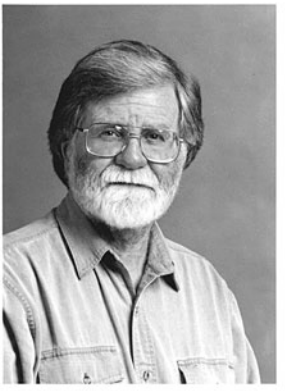


Figure 1.2. The temporal evolution of hypothesis building: time line of the hypotheses of the behavioral correlates of hippocampal theta oscillations. Most ideas can be lumped as reflecting an "input function," such as Grastyán's (left) "orienting response" hypothesis. The most influential "output" hypothesis of theta oscillation has remained the "voluntary movement" correlate by Cornelius (Case) H. Vanderwolf (right). Reprinted, with permission, from Buzsáki (2005b).

I soon realized the impossibility of such a task. Grastyán passionately opposed the term "voluntary" because of its subjective nature, yet he could not avoid its connotations.[36] Vanderwolf used sophisticated ethological, fine-grain analysis of behavior and also tried to distance himself from subjective terms.[37] Paradoxically, with his introduction of the term "voluntary," theta oscillation research uninten-

36. Grastyán dedicated the last decade of his life to understanding the neurophysiological substrates of play behavior and concluded that theta is an invariant correlate of play. According to Huizinga (1955), Grastyán's favorite philosopher, play is "a voluntary activity or occupation executed within certain limits of time and place."

37. The long list of alleged cognitive and behavioral correlates of theta oscillations are discussed in Miller (1991) and Buzsáki (2005b).

tionally entered the territory of "intentionality" and free will. Intention and volition, of course, are also part of orienting, attention, and other subjective acts.[38]

Despite seven decades of hard work on rabbits, rats, mice, gerbils, guinea pigs, sheep, cats, dogs, Old World monkeys, chimpanzees, and humans by outstanding colleagues, to date, there is still no agreed term that would unequivocally describe behavioral correlate(s) of hippocampal theta rhythms. Ironically, an inescapable conclusion is that "will" plays a critical role in theta generation. An alternative, and perhaps more sober, conclusion is that our behavioral-cognitive terms are simply working hypothetical constructs that do not necessarily correspond to any particular brain mechanism.

Where do the behavioral-cognitive concepts that contemporary cognitive neuroscience operates with come from? The answer is from Aristotle and his heart-centered philosophy, not brain mechanisms. Aristotle's terms were adopted by the Christian philosophers and were extensively used by both Descartes and the British empiricists John Locke and David Hume. To their credit, they used many of the cognitive expressions only as hypothetical constructs. Concepts such as attention, conception, association, memory, perception, reasoning, instinct, emotions, and the will, better known as William James's list of the mind, became "real" only after James codified them in his famous *Principles of Psychology*.[39]

Today's cognitive neuroscience lives more or less with James's list as its axiomatic system and also follows his top-down strategy. "Everybody knows what attention is," declared James in his attempt to define the shape and form of the concept. To sound more precise and scholarly, he even added the necessary "*genus proximum,*" as required by good old Aristotelian logic: "it is taking possession by the mind."[40] Sure enough, this deductive general-to-specific approach works well as long as the more general term (hypernym), the mind, in our case, is defined a priori.[41] Precise knowledge and a definition of the conscious mind

38. The scholastic concept of intentionality contrasts the relationship between mental acts ("psychical phenomena") and the external world ("physical phenomena"). Accordingly, intention is the defining feature of several mental phenomena because physical phenomena lack intentionality altogether (see, e.g., Dennett, 1987). Intentions, desires, motivation, and beliefs are intentional states with direction (vector), whereas anxiety, depression, and emotions do not have direction (scalar). To be fair, correlating electrical activity with overt movement was not Vanderwolf 's ultimate program (Vanderwolf, 1988, 2003). What we owe him for most is the important teaching that before declaring an abstract cognitive correlate, one should make sure that overt behavior or an intermediate variable is not an adequate descriptor of brain activity. E.g., if as a result of learning an eyeblink response develops, neurons controlling eye movements show a perfect correlation with the learning process but without contributing to it. The current field of human brain imaging could benefit a lot from his teachings.

39. William James's *Principles of Psychology* (James, 1890) is a great monument in American psychology. This two-volume encyclopedic work is as much psychology as it is philosophy.

40. James (1890), p. 403.

41. The most frequently used nominal definition method in Western cultures is the standard dictionary definition (*Definitio per genus proximum et differentia specifica*), going from general (hypernym) to specific (hyponym). Circular definition, in contrast, always requires a context and proceeds by exclusion of co-hyponyms and enumeration of hyponyms. Its circularity comes from the assumption of a prior understanding of the defined set. Using metaphors and especially models can be effective when other definition methods fail (e.g., Cruse, 1986), but they do not always work, either. "The mind is like a . . ."—unfortunately, it is hard to continue from here.

would surely be helpful for working out strategies to understand the other alleged cognitive faculties of the brain, including attention.[42] James's top-down program, applied to contemporary cognitive neuroscience research, would proceed in the following steps. The first step involves finding neuronal correlates of consciousness. The next step requires the identification of the necessary and sufficient neuronal events and the mechanisms responsible for causing the mind's derivatives (i.e., James's short list and other terms). The final step is a mental rotation that involves the assumption that the identified brain processes in fact give rise to the perceived experience of the brain's owner. After all, without brain there is no mind. To me, this program appears to be *applied,* rather than fundamental, research. This strategy assumes that philosophy and psychology have already identified and defined the independent variables (e.g., concepts of perception, volition), and thus, the major mission of neuroscience is to reveal brain mechanisms (dependent variables) that generate them. This constitutes a paradox if we believe that it is the brain (independent variable) that generates cognitive behavior (dependent variable).

One would expect that the discovery versus invention question would have become a cornerstone issue since the birth of neuroscience. Every new discipline, from molecular biology to computational biology, just to name the most recent ones, gained independence by creating its own vocabulary. Why is neuroscience, especially cognitive neuroscience, so different? If James's list was invented by our historical mentors, what are our chances of figuring out how these dreamt-up concepts can map onto neuronal substrates and mechanisms? I suspect the reason why such a debate has not yet erupted on a large scale is because brain-centered research in the cognitive field is nascent and the plain truth is that, to date, brain-derived functions are too scarce for use in a major assault on the traditional approach. There is nothing wrong, of course, with using terms inherited from philosophy and psychology, as long as we do not forget that these are hypothetical constructs. After all, it is the verbal terms that allow for conversations among members of a discipline and that convey messages across the various scientific fields. However, this communication works best if we are able to create a structured vocabulary that restricts terms to unambiguous meaning that can be objectively communicated across laboratories, languages, and cultures without prior philosophical connotations. Concepts can be verified or rejected only by studying mechanisms. This is a difficult task, given the historically charged terms we have inherited from the inventors. Nevertheless, before declaring James's program to be a failure, let us see what else has been offered.

42. A recent honest and respectable attempt to define the neuronal correlates of consciousness is Koch (2004). An argument in favor of the utility of such a top-down approach is molecular biology. Imagine the Babel of vocabulary in biology without the discovery of DNA. Once the "code of the mind" is defined, the taxonomy of cognitive functions can be vastly simplified, and all cognitive faculties can be derived. I suspect the great success of the molecular biology model is the driving force behind the "consciousness" program advocated by the two Nobel Laureates Gerald Edelman and the late Sir Francis Crick.

More Top-Down

Alan Turing was a fine mathematician and a professional code breaker. But the world remembers this eccentric young Cambridge don for his imaginary machine that, according to him, could replicate logical human thought.[43] Turing confidently claimed in 1950 that machines could match wits with humans by the end of millennium. His top-down strategy was straightforward: comprehension of the mind could be achieved by purely computational theories, without concern for the details of their implementation details. This approach is even simpler and more straightforward than the philosophy–psychology–neuroscience lineage. It offers a seductive shortcut by avoiding the very difficult task of deciphering the brain hardware. To understand the brain, claimed Turing, all we have to do is to simulate its numerous functions by just writing enough code.[44]

To emphasize his seriousness about machine intelligence, Turing offered a test: a machine is intelligent if, in conversing with it, one is unable to tell whether one is talking to a human or a machine. Turing's followers, the artificial intelligence community, produced fancy and important results, such as chess-playing programs that beat the best masters of the art and useful speech and character recognition systems. Nevertheless, these remain in the domain of carefully crafted algorithmic programs that perform a specific task. Human-made machines and the algorithms used to run them are designed for obedience rather than originality. They never come up with an entertaining joke. Neither the ever-more powerful computers nor increased software sophistication has yielded anything resembling a thinking machine. The disillusionment with the "artificial intelligence" approach to the mind is reflected not only by technical criticisms but also by the epistemological dispute that has emerged in parallel.[45] Jerry Fodor of Rutgers University, the most influential philosopher related to Turing's computational

43. Today's visionaries talk about the emergence of a "global brain" for processing and storing information (e.g., Barabási, 2002). Kurzweil (1999) goes even further by giving a timetable for the Worldwide Web to become self-aware. The discussion about the hippocampal "search engine" in Cycle 12 should make it clear why such claims remain ludicrous for a good while. HTML-based web communication is strictly feedforward, and without feedback connections neither oscillations nor higher order phenomena can emerge. For further pro and contra arguments of "Internet's mind," read, e.g., Johnson (2001).

44. Turing (1936). In neuroscience, David Marr was perhaps by far the most explicit follower of Turing's program. For Marr, computer implementation of a problem was a reasonable proof for a similar algorithm in the brain (Marr, 1982). The fallacy of the Turing program, in my mind, is the failure to distinguish between substrate-free concepts and substrate-dependent mechanisms.

45. The term "artificial intelligence" (AI) was coined by John McCarthy at the Massachusetts Institute of Technology in 1956. In AI, the programs "live" independent of their realization in brain or machines, somewhat analogously to the Hegelian spirit or Cartesian soul. Today, AI research is focused on more pragmatic issues, e.g., voice and pattern recognition, expert systems, robotics, neural networks, and computer games. A great victory for AI research occurred in May 1997, when IBM's supercomputer Deep Blue defeated world chess champion Gary Kasparov. Of course, one might argue that the computer was not "playing" chess but simply obeyed the algorithmic steps programmed by its designers.

theory of mind, noted recently that "so far, what our cognitive science has found out about the mind is mostly that we don't know how it works." To add insult to injury, he added, "the main achievement of cognitive science has been to " 'throw light on how much dark there is.' "[46] Disregarding the nuts and bolts of the substrate often leaves us with so many alternatives that testing all options becomes impractical. I think it is safe to conclude that even the über-enthusiasts who repeatedly make hubristic claims about soon conquering the "last frontiers of human understanding" agree that the top-down approach *alone* is unlikely to crack the mysteries of brain algorithms. Nevertheless, Turing's program added a novel aspect to our thinking about the brain: how complex patterns, in our case spontaneous brain activity, may come into being by following simple algorithmic rules (Cycle 5).

Bottom-Up Progress and Reverse Engineering

Despite the obstacles to understanding the brain, today's neuroscientists have reached a general consensus on the strategies to pursue. To grasp the complexities of brain operations, we need a detailed and systematic understanding of at least three main ingredients: the dynamic structural organization of the brain, the physiological workings of its constituents, and the computational mode of operation that enables its neurons in the given anatomical hardware to execute behavior.[47] If the top-down approach advocated by James and Turing is not adequate, let us try to build up function from the bottom.

An alternative or, more precisely, complementary strategy to get an insight into the operations of a system begins with the substrate from which it emanates. Albert Szent-Györgyi formulated this approach plainly: "If structure does not tell us anything about function, it only means we have not looked at it correctly."[48] The technical term characterizing such a working philosophy is reverse engineering.[49] In practice, reverse engineering is taking apart an object to see how it works in order to duplicate the object, often changing the parts but without altering their

46. Fodor (2000). pp. 36 and 125.

47. The philosophical claim of this practical reductionism is that the whole cannot be understood completely without understanding its parts and the *nature* of their sum.

48. András Lörincz, personal communication.

49. Forward engineering begins with the requirements and goals, followed by the design and implementation stages. Most computer networks are designed this way, with a clear function to be implemented, using existing principles and formulas learned previously from other fields. In reverse engineering, the process begins with the end product (e.g., the brain), and the task is to figure out how the components and their relationships gives rise to its function. The major difficulty with reverse engineering is that the implementation of the device's programs may contain unknown principles that must be discovered first. Understanding the Egyptian hieroglyphs was done using the principles of reverse engineering.

true function. Continuing with our car analogy mentioned earlier, one can disassemble a Lotus Elise and examine its engine, brakes, steering, transmission, and other components for the purpose of manufacturing a similarly performing sports car. To be successful, in the process of reverse engineering one has to understand how the components work separately and as part of the car.[50] Applying this philosophy to neuroscience research, deciphering the functions of the nuts and bolts of the brain holds great promise for the ultimate understanding the whole brain. Detailed knowledge of anatomical connections, biophysical properties of neurons, pharmacological features of their connections, and the rules that govern their operations can be built up systematically. The eventual synthesis of all this knowledge is expected to explain the workings of the brain and the consequent subjective experience that springs from it.

The political-military wisdom *divide et impera* is an effective tactic in science as well. When confronted with a very complex problem, a sensible way to crack it is to divide the complexity into manageable subproblems and defeat each of them individually. One practical area where reverse engineering has been exploited repeatedly is the interpretation of brain waves and rhythm. As alluded to above, brain waves are the large-scale representations of the interactions among myriads of neurons, a collective-order parameter. Although they do show a predictable relationship with overt and covert behaviors, without an explicit demonstration that they are necessary for the brain's performance, skeptics may dismiss their importance by claiming that they are just the epiphenomenal wiggling of the jelly brain. Such a challenge can be dismissed only by examining the neuronal content of brain waves within the framework of reverse engineering, an important topic addressed in Cycles 10 and 12. How far can we get with the bottom-up strategy of examining neurons first in isolation, local networks in small slices of the brain, and then interactions between networks in conveniently anesthetized preparations, constantly building on knowledge gained at a lower level and moving up? This approach provides comfort because causal explanations may be reached at every level—*separately.* And this is the crux of the problem. It is almost certain that the bottom-up strategy *alone* will never provide a full explanation for the most complex operations of the brain. The reason, as the reader might predict by now, is that the brain is a nonlinear device: break it up into its components and you will never be able to put them back together again into a functional whole. The full behavior of each component is not contained within the component but derives from its interactions with the whole brain. Global network operations cannot emerge from uncoordinated algorithms. We need to be in possession of the overall algorithm, the "brain plan," to understand the meaning of local processing. This leads us back to William James. If we knew the "big plan," the mind, in the first place, the rest would be easier.

50. The car is a complicated but not complex system by definition. The car is a linear combination of many components, which are combined and used in a predictable way, according to its blueprint design.

Outside-In and Inside-Out Strategies

A successful program in neuroscience has been probing the brain with sensory inputs and examining the reaction of its neurons one at a time, known as single-cell physiology. David Hubel, Thorsten Wiesel, and Vernon Mountcastle applied the single-neuron recording technique to the neocortex of cats and monkeys with stunning results. With their elegant experiments, a new era of sensory cortex research was ushered in. The greatest appeal of such an approach is its simplicity and the ability of the experimenter to control the inputs. By recording the neuronal responses to controlled inputs, one can begin to develop ideas about how the presented stimuli are transformed into a neuronal representation.

Nevertheless, there are two fundamental problems with this outside-in feedforward strategy. First, such input-output analysis of neuronal networks is complicated because the brain does not simply represent the environment in a different format. Features of the physical world do not inherently convey whether, for a brain, a situation is familiar or novel or whether a stimulus is pleasant or repellent. What we may call unaccounted-for variability is perhaps in fact these very attributes embedding themselves in the neuronal responses to sensory input (Cycle 9). Viewing it differently, the reason for this variability is that single neurons are not independent elements in a feedforward stream but are embedded in networks whose state exerts a strong and varying influence on its neurons. In other words, the brain constantly feeds "information" to the recorded single neuron in the form of spontaneous activity, and this variability cannot be accounted for by the input-output analysis of stimulus–single-unit relationships. Ignoring such brain-derived variability would be a great loss since this spontaneous coordinated variability may be the essence of cognition, as I argue in several Cycles of this book. The ensemble activity of neurons reflects the combination of some selected physical features of the world and the brain's interpretation of those features. Even if the stimulus is invariant, the brain's state is not (Cycle 10).

Another problem with the outside-in approach is the uncertain provenance of biologically relevant stimuli. The "simple" stimulus is an abstraction, and the stimulus configuration presented to the brain in research laboratories may be remote from what neuronal circuits are optimized for. Again, this problem becomes increasingly more serious as one attempts to interpret neuronal responses several steps removed from sensory inputs. Oftentimes, neural activity is shaped entirely by the past experiences of the brain. Inspection of a wedding ring may bring up memories of the pleasures of a wedding or the sorrows of a funeral, depending on one's past associations.

An alternative to the outside-in approach is to begin the explorations with the "default," relatively unperturbed brain states and with structures that possess high levels of autonomy. This inside-out strategy does not require a priori knowledge of the relevant stimuli because the focus of the inquiry is on the relationship between the single neuron constituents and the emergent functions generated by their network-level interactions. In the process of exploration, once correlations

are established, it is possible to perturb them in an attempt to discover the hints of causality. I follow this inside-out approach in this volume not because it is the best or only good method but because I have the most experience with it. Furthermore, self-generated behavior and emergent large-scale oscillations tend to occur in the unperturbed brain; therefore, this approach is also more didactic. Accordingly, in Cycles 7 and 8 I discuss the ultimate self-organized brain behavior, sleep, and its possible functions, followed by Cycles 9–12, which are dedicated to the waking brain and its interactions with environmental inputs. The agenda of Cycle 13 is to illustrate the intimate relationship between structural connectivity and global function.

Scope and Coverage

A quick glance through the Cycles makes it clear that the title *Rhythms of the Brain* is a bit grandiose relative to the modest content of the book. Many important topics are omitted or glossed over. The vital oscillations generated by the spinal cord and brainstem are completely ignored, and the bulk of the discussion is centered on cortical systems of the mammalian brain. Circadian and other long-period oscillations are discussed only as they pertain to the faster neuronal events. Until recently, most other brain oscillations have had a bad reputation, associated with such ailments as epilepsy, Parkinson's disease, Huntington's disease, essential and cerebellar tremors, coma, and psychiatric diseases. Each of these topics would deserve a separate volume. Even after all these exclusions, however, there is still a lot to talk about. Rhythms are an essential part of normal brain operations, and my goal is to convince the reader that neuronal oscillations are a fundamental physiological brain function. In turn, I hope that these foundations will serve future progress in understanding pathological rhythms and drug-induced changes on brain oscillations, both beneficial and deleterious.

The Best Strategy

The discovery versus creation question of cognitive neuroscience does not have an easy solution. When I criticize the shortcomings of introspection, philosophy, and psychology, on the one hand, and reverse engineering and reductionism, on the other, I do so not to condemn them but to emphasize the point that there is no single good strategy to solve all complex problems. The "best" approach for progress always depends on the techniques available and the testability of the concepts developed. The methods used, in turn, largely determine what types of questions are asked for further inquiry. It is fair to state upfront that a unifying theory of the brain or the mind that could lead the way is not on the horizon yet. This does not mean that we should not strive to build one. The topics discussed in this book—emergence of spontaneous order, oscillations,

synchrony, structure–function relationships, and representation and storage by cooperating cell assemblies—represent the middle grounds of brain activities between the microscopic mindless neurons and the wise, performing brain. My goal is to disclose how the brain gains its smartness from the organized complexity of its constituents. What follows is a progress report on the fascinating endeavors of neuroscience, a tour of fields that are usually not linked together in a single piece of scientific writing.

Cycle 2

Structure Defines Function

> Architecture is the will of an epoch translated into space.
>
> —Ludwig Mies van der Rohe

If we could document all the connections and wiring patterns in the brain of an individual, would we understand how they give rise to her behaviors?[1] This is a teasing question physiologists love to pose to hard-working morphologists. The answer, of course, is no, with some qualification: we can never discover brain computation without revealing its basic connectivity. Understanding the performance of the brain requires a two-pronged approach. First, we need to know the basic "design" of its circuitry at both microscopic and macroscopic levels. Second, we must decipher the rules governing interactions among neurons and neuronal systems that give rise to overt and covert behaviors. The complexity and precision of brain wiring make an experimental approach absolutely necessary. No amount of introspection or algorithmic modeling can help without parallel empirical exploration. Understanding the principles of neuronal connectivity is important because this knowledge can guide our thinking about implementation of function. Wiring a small number of neurons is relatively straightforward, whereas the task of cabling the human brain is comparable to connecting all stars in the universe. If the brains of all species were uniquely connected in fundamentally different ways, the task would be hopeless. On the other hand, if connections

1. The term "wiring" is used synonymously with axonal connections but with the important qualification that the fine connectivity in the brain is flexible and perpetually changing. As a result, no two brains have identical connectivity, in contrast to the rigid, blueprint-determined wiring of machines.

among neurons follow the same general algorithmic rules across species, progress and understanding may be possible. Once in possession of such rules, we can begin to understand how functions established in small brains can be preserved or exploited for other uses over the course of evolution as brain size grows. This is the scaling problem of neuronal wiring, the main topic of this Cycle. Here, I focus on the general problem of large-scale connectivity, as it applies to the mammalian cerebral cortex.[2] The architectural rules and constraints presented are believed to determine the local and global computation of the cerebral cortex.

The Basic Circuit: Hierarchy of Multiple Parallel Loops

A universal function possessed by all brains is to move the body. Moving specific body parts or the whole body can be useful even in the absence of sensory information of biologic importance. Living in seawater with abundant food around, a simple rhythmic movement was sufficient to feed the simplest animals. Once movement control was in place, these simple organisms began to develop sensors that more efficiently guided movements for finding food, avoiding harmful stimuli and adjusting activity patterns to the day/night changes of light so as to maximize survival.[3]

The basic circuit capable of the aforementioned control functions is recognizable in all vertebrate brains, small and large. During the course of evolution, the basic circuit is not fundamentally modified, but instead, multiple parallel circuits, consisting of intermediate and longer chains of neurons, are superimposed on the existing wiring. No matter what fraction of the brain web we are investigating, neuronal loops are the principal organization at nearly all levels. A physicist would call this multilevel, self-similar organization a fractal of loops.[4] In

2. This Cycle is not meant to be an exhaustive description of the organization of the different cortical regions but concentrates on the fundamental rules of local vs. long-range connections. The architecture of the neocortex is contrasted to the "random space" of the hippocampus in Cycle 11 and the strictly local connectivity of the basal ganglia and cerebellum in Cycle 13.

3. Such capabilities are also present in single-cell organisms, e.g., *Paramecium caudatum* or mammalian sperm cells.

4. Fractals are usually defined in statistical or qualitative terms, loosely including anything that "looks like itself " when magnified in space or time. According to Benoit Mandelbrot, who coined the term "fractal geometry," it is the geometry of deterministic chaos. Fractal graphics are excellent examples of reverse engineering translating the shapes of irregular objects into mathematical formulas, from which the entire image can be reconstructed. Because, by definition, any piece of the fractal geometric design contains a miniature of the entire design, fractals can be completely described by one piece of the design and a rule that determines how the contiguous pieces fit together. The scale invariance of fractals implies that knowledge of the properties of a model system at any scale can be used to predict the structure of the real system at larger or smaller scales (Vicsek, 1992; Mandelbrot, 1999; Barabási and Stanley, 1995). Applying this knowledge to neuroscience, knowing the fundamental properties of the organization of the cerebral cortex in any mammalian species and the rules of network growth, the principal structural organization of smaller and larger brains can be predicted.

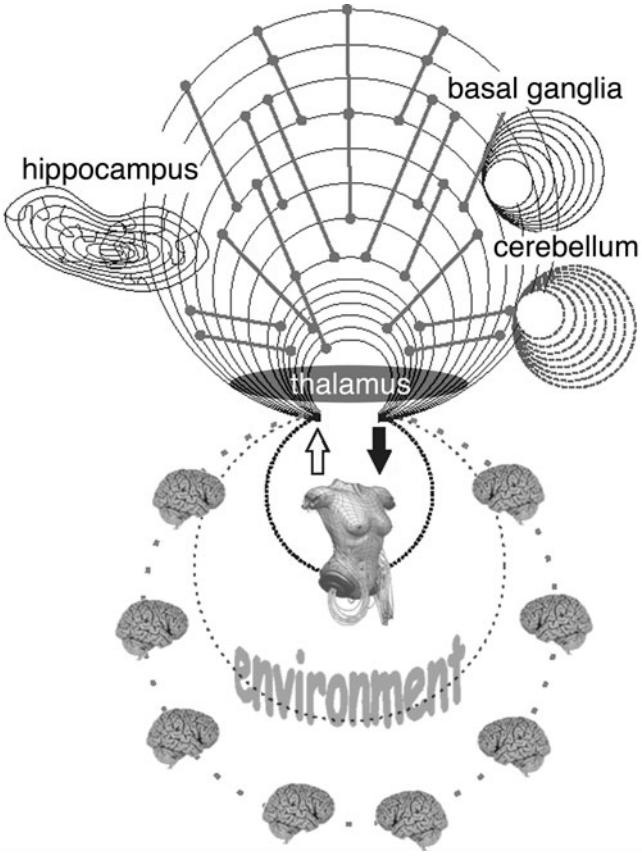


Figure 2.1. The brain is organized in a hierarchy of multiple parallel loops. Intermediate- and long-range connections link the various loops in the cerebral cortex. Sensory information passes through the thalamus, which is under the control of neocortical feedback. The hippocampus provides a relatively random synaptic space. The strictly parallel loops in the basal ganglia and cerebellum are mainly inhibitory. The main pathways are genetically determined, but fine-tuning of connections ("calibration" by the output–input match) is under the supervision of the body, environment, and interactions with other brains.

addition to the multiple parallel loops, links between lower and higher layers are formed, generating a hierarchical form of organization among the parallel loops (figure 2.1).

Building a house from scratch is often easier than expanding it. In principle, this truism would apply to the brain, as well, if brains were to be built by some a priori design. However, no blueprint is available for the brain of any newly evolved species. "New" brains are modified versions of older ones, and the new brain carries the major features of all previous versions. Much like the various layers of an archeological site, the oldest circuits of the brain are located at the

bottom. Subsequently developed levels rest in an intermediate position, while the most recently developed structures are situated on top. These parallel layers or loops interact with each other. The evolutionarily more recent layer can suppress the progression of neuronal impulses in the short (older) loops and reroute the traffic to the longer, higher level loops. From this evolutionary perspective, the main difference between the brains of simple and complex animals is merely the number of neuronal loops that link the outputs to the inputs. In simple brains, there are few neuronal steps between sensation and action, whereas in complex brains, the number of neuronal steps through which activity passes can vary from short through intermediate to long loops. Such simple quantitative details of neuronal organization can largely account for the different responses of phylogenetically older and younger organisms to the same physical world.

Take the example of an unexpected loud noise that produces a startle reflex, which involves the sudden contraction of many of your muscles. The neuronal circuit responsible for such an ancient but important reflex, present in all mammalian species, is simple and well understood.[5] However, the same kind of loud sound embedded in a different context, for example, the timpani in Handel's *Messiah,* may induce a totally different reaction in the human brain. First of all, no startle is elicited. Instead, the sound waves in your ears may trigger neuronal representations of previous memorable performances. The circuitry involved in the latter process is quite elaborate and not well understood. In short, the same physical input can evoke very different outputs in complex brains, depending on the context in which the stimulus is presented. It is important to emphasize again that there is nothing in the physical world by itself that would predict a priori the response of the brain to a stimulus. It is often largely the state of the brain that determines the behavioral outcome. We all know this. What we do not know, however, are the neuronal processes underlying the word "state." A part of this volume is devoted to the exploration of this term.

Before proceeding further, we need to take another look at the loop organization. The loops are not closed by brain wiring, but there is a "gap" between the neuronal connections controlling the outputs and inputs that transmit information

5. Startle reflex is an involuntary reaction to a sudden unexpected stimulus, which involves flexion of most skeletal muscles, a blink, and a variety of visceral reactions due to activation of the midbrain paleocircuits. The latency of the acoustic startle reflex in the rat is a mere 8 milliseconds, measured from tone onset to the beginning of the electromyographic response in the hind leg. This extremely short-latency response involves the auditory nerve, ventral cochlear nucleus, nuclei of the lateral lemniscus, nucleus reticularis pontis caudalis, spinal interneurons, lower motor neurons, and muscles, all connected by fast-conducting fibers (see Swerdlow et al., 1999). An even simpler reflex is the patellar reflex, which involves just one synapse in the spinal cord between the dorsal root ganglion sensory neurons and the large motor neurons of the ventral horn of the cord. Activity in the superimposed loops can often suppress the effectiveness of the patella reflex, e.g., by attending to it. In amphibians, reptiles, and birds, sensory-motor switch time is brief, depending on one or two synapses, and the responses are more predictable (Bullock and Horridge, 1965) because there are only a few longer superimposed loops that can interfere with the stereotypic, species-specific responses.

from the sensors.[6] The gap may be closed by actions exerted by the brain on the body and the environment, a process that "calibrates" neuronal circuits to the metric of the physical world and allows the brain to learn to sense. As a result of this supervised teaching by the actions, the sensors can be directed meaningfully and effectively. The ultimate outcome of this calibration-teaching process is that from past experience the brain can calculate the potential outcomes and convey this prediction to the effectors (e.g., the skeletal muscles). The consequences of this action–brain–sensors arrangement on brain development is discussed in Cycles 8 and 11.

Large-Scale Organization of the Brain Web

In any freshman course on the gross anatomy of the brain, one learns that the human brain has about 100 billion (10^{11}) neurons with an estimated 200 trillion (2×10^{14}) contacts between them.[7] We also learn that, although neurons are sparsely connected, they are within a few synaptic steps from all other neurons.[8] What one does not learn is the general principles of organization that govern this complex connectivity.

Although brain structure has been studied by generations of brilliant minds,[9] the interconnection issue and especially its relation to function have remained an unsolved mystery. Let me briefly outline the heart of the problem and then examine it in some detail. Suppose that nature introduced a useful nervous function, for example, a mechanism for controlling muscles. Because the contraction speed of vertebrate muscles is determined by the properties of myosin, a contractile protein similar in all mammals, the speed of muscle coordination should be largely

6. The central long-range loops between motor and sensory areas (serving the *reafferenz prinzip* or corollary discharge) are likely formed under environmental supervision (see also Cycles 7 and 8). These motor to sensory projections serve to distinguish, for example, movements of the visual world from self-controlled movement of the eyes or head.

7. Estimates for the total number of neurons in the human brain vary between 10 billion and 1 trillion (Williams and Herrup, 1988). Of these, the number of neocortical neurons ranges from 15 to 31 billion. Other forebrain structures, including the hippocampal region, basal ganglia, and thalamus, contain an additional 5–8 billion, and fewer than 1 billion are in the brainstem and spinal cord combined (Shariff, 1953; Lange, 1975; Pakkenberg and Gundersen, 1997). The largest variability in the total number estimate involves the uncertainty about the number of granule cells in the cerebellum, ranging from a few billion to 70 billion (Braitenberg and Atwood, 1958; Lange, 1975). Some other species have more neurons than we do. The 6,000-gram brain of the elephant may have two to three times as many neurons as does a 1,350-gram human brain (Jerison, 1985; Martin and Harvey, 1985). For the distribution of neurons in various structures and other quantitative anatomic data, an excellent source is Blinkov and Glezer (1968).

8. Synapses are the structural links between neurons that allow for unidirectional communication between neurons (Peters et al., 1991).

9. For example, Ramón y Cajal (1909–1911), Nauta and Feirtag (1979), Szentágothai (1978), Braitenberg and Schütz (1998), Allman (1999). In addition, more than 20,000 anatomical papers have been published on the problem of brain connections.

preserved across species, independent of the size of the nervous system.[10] Several other temporal aspects of the physical world affect various mammals similarly; therefore, often small and large brains must have to deal with problems of more or less the same temporal scale.

While a general solution for temporal scale preservation may be trivial for an electronic device where electric pulses travel at the speed of light, the slow conduction velocity of neuronal connections in the brain poses a challenging problem for preserving the time necessary for getting from one neuron to any other, because in larger brains neurons are inevitably spaced further apart. In general, the problem we have to address is how to preserve the temporal windows of action and perceptions for functions to remain useful in brains of various sizes. As discussed in Cycle 6, the frequency bands of the various brain oscillators are kept relatively constant throughout mammalian evolution even as the numbers of neurons and their connections have increased enormously. The problem of preserving a function and performing it at a constant temporal scale while multiplying the number of contributing neurons does not have a straightforward solution. If all neurons in the cerebral cortex are to be given an equal chance to contribute to a global function, how should they be connected in small and very large brains? The general principles of neuronal organization have yet to emerge. Nevertheless, we can compare some brain facts with other known connected systems and learn something along the way. Let us begin with the problem of connectivity.

Scaling Problems in Brains of Various Sizes

Let us go back to the 10^{11} neurons that are packed in our skull volume of 1.5 liters. Each neuron is a complex device, perhaps the most complicated cell type nature has created. Neurons are treelike structures with branching patterns ranging from those of small bonsais to the giant sequoias. This structural intricacy has developed as an elegant and effective way to maximize the receptive surface area for connections from other neurons. To further increase the number of sensors, the branches, called dendrites, are covered by numerous spines in most neurons. By growing branches and spines, a neuron can create between thousands and tens of thousands of receptive contact sites, called postsynaptic receptors. Spine density and the extent of dendrites vary somewhat in brains at different levels of mammalian evolution, but not much. The most prevalent neuronal type of the cerebral cortex, the pyramidal cell, has 5,000–50,000 postsynaptic receiving sites. It is through these appositions or synapses that neurons connect to each other. In the human cerebral cortex, 90 percent of connections are established with other neocortical pyramidal cells.

With this new information, we can generate another number. Assuming just

10. Myosin is a contractile protein found in skeletal muscles. Human myosin is only twofold slower than the myosin of the 100-fold smaller rat (Szent-Györgyi, 1951).

5,000 connections per neuron, all neurons in the human brain (10^{11}) would have about 5×10^{15} connections via their thin and long processes, called axon collaterals. Axons typically emerge from the cell body and take a long, convoluted journey to reach a few dozen or tens of thousands of nearby and distant neurons. Axons occupy much more volume in the brain than do the cell bodies, dendrites, and spines combined. However, we cannot afford the luxury of using all of our skull space for only neurons and their connections. Neurons, including their axons, are surrounded by numerous glial cells and an extensive brain vessel system.[11] These supporting structures require a lot of space. In fact, the real computational elements of the brain, the neurons and their connections, occupy less than a liter of volume.

For the moment, let us put aside the physical details and see how we can proceed with the issue of connectivity using the knowledge available to us from mathematics. For the sake of simplicity, let us start with just 50 neurons. To link each of these neurons to all other neurons would require 1,225 bidirectional connections. But we know that this is not the brain's choice. Neurons are not connected to all other neurons but only to a fraction of them. What is the minimum number of links that can connect each neuron to at least one of its partners? The general solution to this sort of a problem is the most famous in graph theory.[12] It took the genius of two mathematicians, Paul Erdös and Alfréd Rényi, to solve this puzzle.[13] They showed, that using just 98 randomly placed links, a mere 8 percent of the 1,225 all-to-all connections, we can connect all 50 nodes (neurons). Of course, the math underlying random graph theory provides a solution for fully

11. Without the support of glial cells, neurons cannot survive. Furthermore, neurons are hungry and must be constantly fed. For this reason, the brain is supplied by the highest density of blood vessels in the body and uses 20 percent of the body's blood-supplied oxygen and energy nutrients 24 hours a day, 7 days a week, even during sleep. The energy consumption of the newborn's brain is even more telling. As much as 40 percent of the body's energy resources are devoted to the developing brain. Even during hibernation, in those animals that can afford this luxury, brain metabolism is not reduced appreciably (Meyer and Morrison, 1960).

12. A graph is a symbolic representation of a network, defined abstractly as a set of linked nodes. A node (also called vertex) is a terminal point or an intersection point of a graph, e.g., a neuron. Nodes are connected by edges or links, e.g., an axon. In brain networks links are directed. The path is an uninterrupted sequence of links. Finding all the possible paths in a graph is important to assess the flow of traffic from node to node (in our case, neuron to neuron).

13. The first graph problem was first formally posed by the town folks of Königsberg: how to walk across the seven bridges erected on the two branches of the Pregel river without crossing one twice. The bridge problem was solved by the Swiss-born mathematician Leonhard Euler. Euler provided a rigorous mathematical proof: it is not possible. What began as a simple mental exercise for Euler gave birth to a new branch of mathematics: graph theory. A random graph (Erdös and Rényi, 1959) is one in which one begins with n isolated nodes and makes a pass through the graph considering, for every possible link, whether or not to create a link there, based on some probability p, where p is between zero and one, inclusively. If $p = 0$, all n nodes remain isolated and no links are formed. $p = 1$ refers to a complete graph, where every node is connected to all other nodes through at least one node. Connectivity can be made to be sparse by reducing p. Random graphs do not form clusters, i.e., groups of highly connected nodes. For an introduction to graph theory, I suggest Hayes (2000a,b). The detail-rich graph book Bollobás (1985) is among the most frequently consulted by graph theorists.

connecting any number of neurons. The good news is that with increasing numbers of neurons, the fraction of the links required to connect nodes to the graph drastically decreases. For example, for 1,000 neurons only 1 percent of all possible combinations are needed to connect every one. For a billion neurons, the number of links is less than 0.000001 percent of the possible total. Thus, building larger and more complex brains with ever-increasing numbers of neurons does not require a linear increase in connectivity, although it still requires a staggering increase of wiring.

Now, in principle, we can easily wire up 10^{11} neurons with the available 5×10^{14} synapses so that no neuron is left out. In a random graph system, if each neuron receives, say, 100 inputs, each neuron should give rise, on average, to 100 outputs, since the total convergence and divergence are identical. Based on the divergence of an average cortical pyramidal neuron, each neuron can transmit information to 5×10^{3} randomly selected peers. The second-order neurons, connected randomly to their 5×10^{3} peers, will connect us to 2.5×10^{7} targets in just two steps (synapses). Thus, according to the mathematical foundation of random graphs, we can get from any neuron to any other neuron in the human brain through just three synapses.[14] By now, anyone who has read the book or seen the movie *Six Degrees of Separation* or is familiar with such websites as the Erdös Number Project may think that there is some parallel between the brain web and these entirely different worlds.[15] The sophisticated reader should suspect, however, that something went grossly wrong with the logic somewhere.

Our quick navigation through the jungle of the brain, using just three synapses, appears too good to be real. Three degrees of neuronal separation are better than the five or six synapses neuroanatomists have previously guessed. This discrepancy is not such a big problem, however, because the neuroanatomists' six synapses refers to the claim of connectivity "from anywhere to anywhere," that is, the worst-case scenario. The mean degree of neuronal separation, therefore, should be smaller. So the error of the underestimation must have occurred elsewhere. In abstract mathematical space, connecting a node to neighbors or to any distant nodes is done with equal ease, because there are no neighbors and distant partners, and no physical wiring needs to be laid down. But connecting neurons randomly in real physical space would require a lot of expensive connections and a very large skull to hold together all the wiring. Furthermore, we know for a fact that neurons in the visual cortex, for example, are not randomly connected to just any other neurons locally, or to the auditory cortex, motor cortex, or the frontal part of the brain. We also know that most connections among neurons are local in most brain structures.

14. Interestingly, this misguided thinking about random graphs led Braitenberg and Schütz (1998) to postulate that "any two neurons may communicate with each other via no more than 2 or 3 interposed neurons" (p. 193). This statement is quite surprising since they emphasize the fact that most cortical connections are local.

15. In the Erdös number graph the nodes are mathematicians, and a link connects mathematician *X* to mathematician *Y* if *X* has written a paper with *Y*. The Erdös number of *X* is the length of the shortest path in this graph connecting *X* with Erdös. (see http://www.oakland.edu/enp/).

Using mostly local connectivity we can build a graph different from random graphs. In this new graph, local clustering can be very high. Now we face a different dilemma. In a graph with connections only between neighboring neuronal clusters, it would take literally thousands of synapses to navigate from a neuron in the visual part of the brain to a muscle-controlling neuron in the motor cortex. For a brain using many serially connected neurons, sensing a fast-approaching object and avoiding it by controlling the appropriate body muscles would be a hopeless effort because the conduction velocity of pulses is very slow in the axon. Numerous serial synaptic steps and the long time involved may also defeat the main computational advantage of the cerebral cortex: sharing locally computed information with all other neurons.

Thus, two organization principles—the degree of local clustering and the degree of separation between the distant parts of the brain (let us call it synaptic path length)[16]—compete with each other. Random connections can shrink the degrees of separation, whereas the density of local connections increases the clustering effect. It appears that we need both types of connectivity in the cerebral cortex so that efficient large-scale traffic can be accomplished with a minimum amount of wiring.

Anatomists have known for quite some time that the majority of local connections are supplemented by long-range connections, although the rules that determine the "optimal" ratio of short- and long-range connections have yet to be discovered. Is this ratio a constant in brains of various sizes, or, if different, can the rule of "optimal" wiring in growing brains be determined? As the brain is scaled up, it is expected that the percent connectedness (i.e., the fraction of all cells with which any one cell communicates directly) should decrease. If the functional connectedness is to be maintained in the face of increased neuron numbers, then the average axon length connecting the neurons will be substantially increased. The result is reduced computational speed due to axon conduction delays.[17]

A potential remedy to the brain wiring problem emerged outside the neuroscience field in the form of a three-page paper titled "Collective Dynamics of 'Small-World' Networks" published by Duncan Watts and his graduate advisor, Steve Strogatz, at Cornell University.[18] The crux of their mathematical insight is

16. Synaptic path length is the average number of synapses between randomly chosen neuron pairs (i.e., the length of the most direct route between the most distant neurons). The term "network diameter," used mostly for describing connection access on the Web, is synonymous with synaptic path length. Synaptic path length is different from assessment of path lengths by gross anatomical and fMRI methods, which estimate values between two and three (e.g., Hilgetag et al., 2000; Sporns and Zwi, 2004; Achard et al., 2006). The area-to-area path length is always shorter than neuron-to-neuron path length.

17. One consequence of decreased interconnectedness in larger brains is increased segregation of the neuronal pool. Ringo (1991) suggested that this segregation may be the force for more specialization in larger brains, for example functional differences between the hemispheres.

18. This pioneering paper (Watts and Strogatz, 1998) is an important reading for anatomists and systems neuroscientists. For a thorough airing of the background and the discovery of small-world formalism, see Strogatz (2003). Another readable and personal account of the events leading to the formulation of small-world networks is Watts (2003). Buchanan's small paperback (2003) is yet another easy read on the subject. Small-world networks are basically random graphs with local clustering.

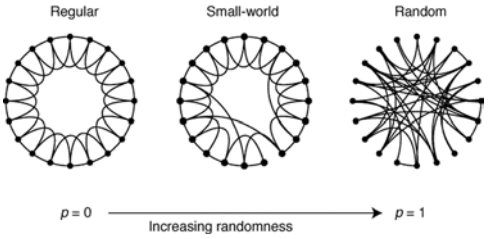


Figure 2.2. Small-word networks combine the advantages of regular local organization and random wiring. Each network has 20 nodes (e.g., neurons), each of which is connected to four other neurons. The synaptic path length (getting from any neuron to any other neuron) is longest in local networks and shortest in random networks. With an intermediate probability of random connections, the small-world network is highly clustered locally, yet has small synaptic path length, similar to the random graph. With increasing numbers of neurons, the proportion of long-range connections required to keep the synaptic path length constant dramatically decreases. Reprinted, with permission, from Watts and Strogatz (1996).

illustrated in figure 2.2. Suppose that each circle is a neuron, and the lines represent axonal connections. If we scale up the illustrated graph a bit so that each neuron is connected to 10 of its nearest neighbors (rather than just four as shown), we will have 5,000 synaptic connections and 0.67 degree of clustering, a measure they introduced.[19] Now, let us replace 50 local connections with 50 new randomly placed links (1 percent of all); the degree of clustering decreases only negligibly (0.65). Nevertheless, the new graph is entirely different in its other properties. Without the 1 percent random but long-range connections, the average synaptic path length (i.e., the degree of neuronal separation in the network) is about 50, which is too long to achieve any useful function given the long axon conduction and synaptic delays. With the few random links added, it drops to 7. The beauty of the new arrangement is that it still preserves some advantageous features of the old random graphs.[20] The number of random links required to keep the synaptic path length short increases much less than the size of the network. In other words, the larger the network, the greater the impact of each random link on the effective connectivity of the network. For 20 billion neurons in the human cerebral cortex, organized mostly in local clusters, a much smaller fraction of long axonal links is

19. Degree of clustering or the density of local connectivity can be characterized by the clustering coefficient, defined as the average fraction of neighbors directly connected to each other.

20. When testing their abstract theory, Watts and Strogatz examined three real-world networks: power lines, the social web of Hollywood actors, and the neuronal net of the nematode *Caenorhabditis elegans.* These examples fit the bill for small-world network architecture. But other real-world examples, including the mammalian brain, do not, as they realized later. In his book *Six Degrees* (2003), Duncan Watts almost apologetically declared: "We made one big mistake. We did not check!" I, for one, am glad they did not. Had they checked and looked elsewhere, they may have conceded defeat and would not have submitted their paper. The scientific community would have been deprived of a great discovery.

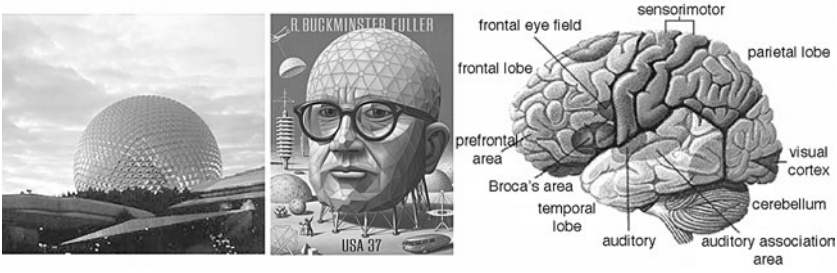


Figure 2.3. The synergy of tension and integrity (tensegrity) provides robust stability to structures. Buckminster Fuller's tensegrity principle is used in many scalable structures, such as the Epcot sphere in Orlando, Florida (left). Right: Major divisions of the left hemisphere of the human brain. The cerebral cortex is also a scalable structure. The cortical and cerebellar surface is increased by numerous grooves (gyri and fissures). Systems defined here are characterized by more extensive long-range connections within members of the system than across systems.

needed to achieve the same short synaptic path length than in the much smaller brain of a mouse (figure 2.3).

At about the time that Watts and Strogatz tried to figure out the math behind their small-world universe, another physicist, Albert-László Barabási, at the University of Notre Dame struggled with a seemingly different problem. He studied the rules of traffic in the World Wide Web. By examining the accessibility of the websites on the Internet, his team realized that traffic is directed mostly toward a handful of busy sites, for example, the search engine Google and the popular e-store Amazon.com. These popular hubs are visited orders of magnitude more frequently than, say, my website. Barabási argued that many real-world networks, including the Web, evolve by some rules but they cannot be described by illustrating a typical, representative example. Instead, the connections in these "scale-free" networks obey a statistical rule called the power law.[21]

Scale-Free Systems Are Governed by Power Laws

In explanations of complex problems, we often provide a persuasive "typical" example that faithfully represents the whole distribution. For example, the brain of an average adult human male weighs 3 pounds 2.2 ounces (1,350 g). Although this number represents the brain size for most people, many have smaller or larger brains than typical. Among famous people, Anatole France's brain had the lowest weight ever recorded for any nonretarded person: 1.11 kilograms. The upper end of the scale is marked by the huge brain—2.01 kilograms—of another novelist,

21. Barabási's bestseller *Linked* (2002) is an entertaining and easy read on the subject of scale-free systems.

the great Russian writer Sergeyevich Turgenev. Ironically, Franz-Joseph Gall, the founder of phrenology,[22] had a very small brain (1.2 kilograms).[23] These individual differences are, however, quite small, and brain weights of humans are pretty much the same, with some minor variations on the left and right, thus creating a bell-shaped curve (i.e., normal or Gaussian distribution). Nobody has a brain 10 times smaller or 10 times larger than that of the average person. This so-called normal distribution is widespread in nature. Its general applicability is a consequence of the central limit theorem,[24] which suggests that if a large number of independent influences contribute to the outcome of some event, that outcome will result in a bell-shaped distribution with a characteristic mean.

In scale-free systems, things are different. In systems governed by power law statistics, there is no peak at an average value, and a select small group can have the largest effect. For example, if we drop a vase on the floor, it will break into fragments of varying size. There will be a lot of debris but also a number of reasonably large fragments. If we collect all the pieces, from the microscopic ones to the large, and plot their numbers as a function of size on a log–log scale, we will get an oblique line: a power law for fractures. No one fragment can be considered as the characteristic size. There is no "typical example" in a scale-free system. A power law implies that there is no such thing as a normal or characteristic size scale and that there is no qualitative difference between the larger and smaller pieces or events.[25]

22. Phrenology (*phrenos* is Greek for mind) or cranioscopy assumes that a person's character and mental capacity can be detected by the external inspection of the skull. The Viennese physician Franz Joseph Gall suggested that mental faculties could be deduced from the sizes and shapes of various bumps and depressions on the skull because the tissue of the brain somehow shapes the hard bone. Gall's early maps on criminals and the insane led to his conjecture of "theft organs" and "murder organs," followed by numerous other terms, e.g., "benevolence," "self-esteem," "conjugal love," "imagination," "religious experience," "wit," "cunningness," and "honesty" (Damasio, 1995). Today, we are witnessing the emergence of a new form of phrenology by searching for the physical locations in the brain responsible for these and other invented terms based on our contemporary imaging methods, e.g., fMRI and PET (see Cycle 4).

23. For brain weights of famous people and related stories, see Gould (1980).

24. The central limit theorem demonstrates that, in large enough samples, the distribution of a sample mean approximates a normal, bell-shaped curve. Essentially, it means that a sufficient number of random samples of independent observations will have statistical properties similar to the populations they were chosen from. The approximation steadily improves as the number of observations increases.

25. A function, $f(x)$, is a power law if the dependent variable, x, has an exponent (i.e., x is raised to some power, hence the name of the law). E.g., for $x=1$, $y=1$; $x=2$, $y=4$; $x=3$, $y=9$, etc., $y=x^2$ applies. I.e., y is a power law in x with a power or index of 2. E.g., if 1,000 neurons have two synaptic connections, then 500 have four, 250 have eight, only 125 will have 16, etc. . Here the index or power is 2, but it can be any small number. Thus, a power law implies that small occurrences are extremely common whereas large instances are rare. In scale-free systems, the rate of decay is much slower than the decay rate for normal distribution, and there is no characteristic peak in the distribution that would characterize mean behavior. Points distributed along a line in a log–log graph are the hallmark of the power law. What makes the power laws so powerful is that they seem to be behind many seemingly unrelated complex systems, e.g., phase transitions of matter, chaos theory, fractals, airport traffic, the

The abstract math behind the power law implies that, instead of the roll of the dice, the events are not completely independent of each other, and a few large events or connection "hubs" dictate the action. To provide an example from the brain, a small collection of cells in the brainstem,[26] called the locus ceruleus, literally meaning blue spot, is such an effective hub in the brain. Its neurons contain and release a substance called norepinephrine, which, when oxidized, turns blue. Each of the 10,000 or so locus ceruleus neurons receives input from only a few hundred other neurons. But their output territory is enormous. They innervate nearly the whole brain and spinal cord. If the firing pattern of these neurons changes, their influence is conveyed to virtually the whole brain. Other examples of hubs in the brain include the cholinergic basal forebrain and dopamine-producing cells of the substantia nigra (meaning black substance).

Because of their widespread influences, these brain hubs are susceptible to targeted attacks of unknown etiology. Once a hub is damaged, the consequence is a large-scale brain dysfunction, such as Parkinson's disease. The amygdala, a hub with numerous cortical projections, is needed for fear conditioning.[27] Impaired neuronal hubs, like their abstract and real-world cousins, can cause clinical problems in at least two different ways: first, by failing to transfer information due to the missing neurons, and second, by propagating potential errors, brought about by the surviving hard-working minority, to a large number of brain sites. As described in subsequent Cycles of this book, the brain has adopted a variety of architectural solutions whose exact descriptions require novel anatomical approaches and new mathematical solutions.

The Tensegrity Plan of the Cerebral Cortex

Before modern times, buildings were constructed from heavy materials according to Egyptian, Greek, and Roman concepts of architecture.[28] However, structures are only as strong as their weakest link. With the traditional concepts and materials,

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size distribution of cities, the connection structure of the Internet, and traffic at various websites (Barabási and Albert, 1999). Viewing things from a broad perspective, small-world and scale-free architectures are fundamentally similar. In a strict small-world network, long-range connections are randomly placed. In scale-free systems, short-, intermediate- and long-range connections are distributed according to a power law distribution. Coexistence of local and global interactions is also ubiquitous in many other systems, living and nonliving (Csermely, 2005).

26. The brainstem is a collective name for structures directly above the spinal cord, including the medulla, pons, and midbrain.

27. Joseph LeDoux of New York University, a pioneer in the study of emotions as biological phenomena, has been studying the role of the amygdala in fear conditioning (LeDoux, 1996).

28. Modern architecture began in the twentieth century with the goal of turning engineering into architectural-aesthetic structure. Rather than simply fusing architecture and engineering, the most beautiful designs arise from the struggle between the two disciplines—Santiago Calatrava's floating roof of the Olympic Stadium in Athens is a beautiful example.

a triple-size replica of Stonehenge or St. Peter's Basilica cannot be built. In other words, these conventional architectural plans are not scalable. Yet, the Louisiana Superdome in Atlanta has a 680-foot-diameter clear-span roof, a feat unimaginable for architects before the introduction of the tensegrity (tension-integrity) concept by Richard Buckminster Fuller in the 1940s.[29] His solution was an astonishingly simple but robust and scalable geodesic design, in fact, nothing more than a series of contiguous triangles or hexagons on a spherical surface, building out from a ring in its pole. The continuous pull (convergence) is balanced by the discontinuous push (divergence), producing an integrity of tension–compression, a win-win relationship.[30] The tension-bearing members map out the shortest paths between adjacent members. Tensegrity structures are omnidirectionally stable and independent of gravity. They do not have a "weakest point," and faults do not propagate, since tension-compression issues are dealt with locally and equally. Theoretically, there is no internal limitation to the size of tensegrity structures. Cities could be contained within them. Remarkably, the same principle provides the stability of the atomic bonds in the geodesic-shaped C_{60}, one of the most stable molecules, aptly named buckminsterfullerene[31] by its discoverers. All these

29. The term "tensegrity" is used in this volume as a metaphor that reflects both structural and dynamic stability of the cortex. Tensegrity in an architectural system stabilizes a structure by balancing the counteracting forces of discontinuous compression and continuous tension. The compression elements of the construct "float" in continuous tension network, as first recognized by the architect-engineer Buckminster Fuller or by the sculptor Kenneth Snelson, depending on which argument you prefer. According to Buckminster Fuller, tensegrity or, as he later preferred to call it, synergetics is a new strategy of design science, which starts with the whole rather than parts, echoing the ideas of Gestalt psychologists (Buckminster Fuller, 1975–1979). The fundamental unit in synergetics is the equilateral triangle (60 degrees coordination) rather than the rectangle of traditional geometry (90 degrees). Buckminster Fuller was likely aware of the works of the evolutionary biologist D'arcy Thompson (1917), who expressed similar ideas. Thompson believed that living structures obeyed engineering principles. For Thompson, form is a mathematical problem, whereas growth is a physical problem. Genetic information provides only a general plan, and the formative power of physical forces determines the final form, depending on the "scale" of the organism. Among his most striking examples is the geometrical transformation of baboon skulls into skulls of other primates or humans.

30. Tensegrity dynamics in brain networks is achieved by the balance between excitatory and inhibitory forces. Dynamic tensegrity provides a magic meaning for the New World shamans through the teachings of Carlos Castaneda (1972). The Yagui shamans in Mexico perceive the world's "floating pure energy" directly by a process they call "seeing." The energy entering the shaman's body converges at the "assemblage point," where pieces of the world come together. The assemblage point is the very spot where perception of the world and "pure energy" are assembled. Although the assemblage point is generally fixed in the body, it can be displaced during sleep and by "volitional dreaming," assisted by a special concoction, containing the divine mushroom of the *Psilocybe* family (the chemical structure of its active ingredient is similar to the neurotransmitter serotonin). During the course of the "seeing" sessions, the shamans go through a series of rhythmic movements and postures, called "magical passes," that kindle volitional dreaming. According to the shamans' belief, these dreams foster the optimum balance between internal states and the "energy of the universe": a tensegrity state, a perfect harmony of opposing forces.

31. Harod Kroto and Richard Smalley, the experimental chemists who discovered C_{60}, the carbon cluster-cage molecule, named it buckminsterfullerene because they intuited that the atoms were arranged in the shape of a truncated icosahedron—Buckminster Fuller's geodesic dome (Kroto et al., 1985).

astonishing features of scalability and robustness are due to a few elementary rules.[32]

The cerebral cortex is a *scalable* and robust spherical structure.[33] Its modular plan is identical in all mammals, with five layers of principal cells and a thin superficial layer containing mostly distal apical dendrites and horizontal axons. These layers are sandwiched together in the gray matter, spanning only 1–3 millimeters in thickness in all mammals. The structural "algorithm" of the cerebral cortex is a multiplication of fundamentally identical hypothetical modules, often referred to as cortical mini- and macro-columns, barrels, stripes, or blobs, with mostly vertically organized layers of principal cells and numerous interneuron types (figure 2.4). It has been suggested that the smallest division of the monkey cerebral cortex that can perform all of the functions of a cortical area is about 1 square millimeter. The number of these basic cortical modules multiplies by more than 10,000-fold from the tiniest shrew to human.[34] The boundaries of the hypothetical modules, however, are often hard to define.[35]

In most body organs, defining a unit of operations is quite useful. For example, the kidney's loop of Henle and the liver acinus are true modules. All modules work in parallel and perform pretty much the same function. In the cerebral cortex, however, modules do not simply operate in parallel but strongly interact. They do not work in isolation but are embedded in a larger structure. Integrative neocortical operations emerge through interactions between the modules rather than within single isolated modules.Yet, the most efficient way for nature to build

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Fullerenes are closed-cage structures. Each carbon atom is bonded to three others, and the hexagonal rings are closed into a cage by two pentagonal rings. The carefully chosen 20-letter term, buckminsterfullerene, is not only an homage to a genius who designed whole systems unpredicted by their parts but also matches the 20 facets of the icosahedron—a letter for each facet.

32. During the Cold War, Paul Baran (1964) worked out a communication network that would endure a large number of breaks. His distributed design is essentially a tensegrity structure. In case of an attack or router/cable failures, the network would reconstitute itself by rapidly relearning how to make best use of the surviving links with the shortest path—a real neuron network-like behavior.

33. Most of our cerebral cortex is isocortex with a six-layer laminar structure. The allocortex (also called heterotypical cortex) has variable numbers of layers. The two types of organization are also spatially segregated. Projecting from the pyriform cortex (where olfaction is processed), a large canyon or equator, called the rhinal (i.e., nose-related) fissure, separates the neocortex from the allocortex. The anatomical details described in this section apply mainly to the isocortex. When the structural and physiological mechanisms apply to both neo- and allocortex, the collective term "cortex" is used.

34. This crude estimate is only for a single location of visual space in the primary visual cortex (Hubel and Wiesel, 1974). However, it takes a much larger brain area to compute an image. The local organization of the neocortex is remarkably similar everywhere, although important differences can also be identified. The overall density of neurons in the neocortex is relatively constant, independent of area (with the sole exception of the primary visual cortex). Each column with 1 square millimeter of cortical surface area contains 50,000–100,000 neurons (Rockel et al., 1980).

35. In principle, a module should include all cell types of the neocortex, including the various classes of interneurons, and the connectivity within the modules should be similar. The boundaries between the modules are difficult to determine because there is a continuity of local, intermediate-range, and long-range connections between the modules, often without any recognizable discontinuity.

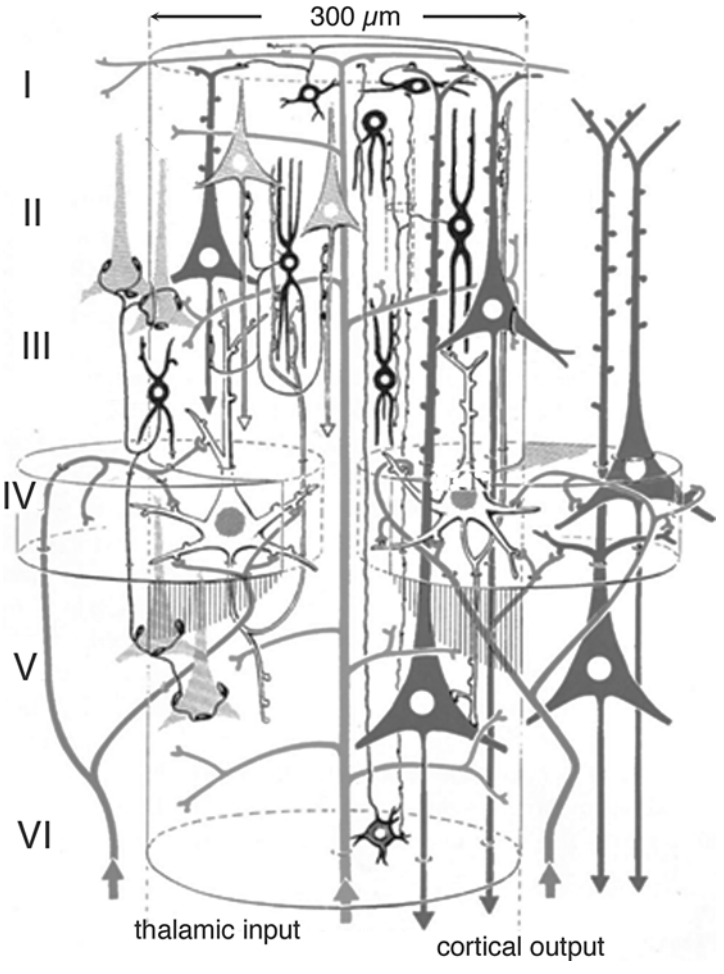

Figure 2.4. The cortical "column." The neocortex is assumed to consist of repetitive functional modules. A functional module presumably contains all major neuron types and connections, typical of all neocortex. The hypothetical modules can perform similar local computation.Roman numerals (I to VI) refer the six cortical layers. Reprinted, with permission, from Szentágothai (1983).

a robustly scalable network is through predominantly local wiring, according to the principles of tensegrity.[36]

Like Buckminster Fuller's tensegrity structures, neurons in most, but not all (see Cycle 11), brain structures attempt to map out the shortest paths with their

36. The primarily neighborhood organization also has an impact on the macroscopic organization of the neocortex. A clever solution for increasing the cortical surface yet keeping the neurons connected with short wires is by folding it. The resulting grooves (or gyri) on the brain's surface result in much of the cortex being buried. In primates, more than half of the cerebral cortical surface is buried

surrounding peers. They receive most information from their immediate neighbors and act locally. Communicating with distant neurons requires costly connections, and transporting electrical pulses over long distances is metabolically expensive.[37] The local order of neuronal connections has important consequences for brain functions. One consequence is that any one neuron's targets have a large degree of overlap with its neighbors' targets. This principle is not unlike our social connections. Friends of two friends are more likely to know each other than are friends of two randomly chosen people.[38] For motor organization, this principle has the consequence of considerably better coordination of adjacent than of distal skeletal muscles, resulting in a neocortical map of the physical layout of the individual muscles. Muscles of the thumb and fingers will have more interconnections in their representation than do, say, muscles of the thumb and toe. This organization is, of course, advantageous since thumb muscles should be better coordinated with physically adjacent muscles of the palm than with those of the foot or tongue. Muscles are thus most economically represented in the neocortex by their geometric relationships in the body. A map of the physical layout of the body surface is also reflected in its neuronal representation. Neurons representing the skin surface of the thumb in the somatosensory cortex are adjacent to those representing the fingers and distant from those representing the skin of the foot. This organization makes sense. An insect crawling on one's hand will stimulate neighboring receptors in a short time epoch at orders of magnitude higher probability than in a finger–toe–nose–finger sequence.[39] As discussed in Cycle 6, neighboring frequencies in human speech are much more likely to follow each other than are sounds with random frequency and power (air pressure) distributions. This likelihood rule is reflected by the tonotopic arrangement of neurons in the auditory cortex. Neurons in the retina, visual thalamus, and cortex combine information representing adjacent parts of the environment much more efficiently

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and not visible directly from the surface. According to David Van Essen at Washington University–St. Louis, the tug-of-war between hydrostatic pressure and the mechanical tension properties of the axons is responsible for the formation of cortical folding patterns (gyri). His tension-based theory (Van Essen, 1997) beautifully explains why strongly interconnected neighboring areas are consistently separated by an outward fold, whereas weekly connected regions are separated by an inward fold. Like a parachute, where the push is exerted to the middle of the canvas by air pressure whereas the ropes pull the edges, the domelike shape of neocortical gyri and cerebellar folia is brought about simply by opposing mechanical forces: a tensegrity solution. It is quite refreshing to see explanatory engineering ideas such as Van Essen's in the molecular biology era of neuroscience.

37. Kalisman et al. (2005) suggest that axons promiscuously touch all neighboring dendrites without any bias. There are many more potential contacts than the actual number of synapses. There are no good methods to determine the exact density of local connections, and the estimates vary from 10 to 90 percent (Miles, 1986; Markram et al., 1997; Thomson and Bannister, 2003).

38. Granovetter (1973). This organization is apparent in the neocortex. When neurons in layer 2/3 are connected to each other, they more likely share common input from layer 4 and within layer 2/3 than are unconnected pairs (Yoshimura et al., 2005).

39. These maps are not simply formed according to some genetically determined blueprint but have to be created by the movement of a body whose morphology constantly changes, especially during early development (see Cycle 8 for discussion of the brain-in-the-body subject).

than nonadjacent parts.[40] The retinotopic topographic representation is preserved beyond the primary visual cortex, although the proportions change systematically.[41] The interconnected maps of the visual system are arranged so that the distance traversed by axon paths, connecting neurons that represent adjacent part of the visual environment, are minimized. This economic compromise of axon wiring is used to explain why higher-order maps get split and folded, instead of keeping an orderly two-dimensional layout.[42]

Imagine a computer screen with random dots appearing in all possible combinations. Even for a low-resolution screen, the possible variations are staggeringly high, yet only a very limited set of the theoretically possible combinations is interpreted as "figures" by a human observer. The rest are simply judged as noise. Of course, there is no a priori reason why some patterns are more meaningful than others. The "meaning" of the pattern is created by the observer. According to Béla Julesz, what makes a constellation of dots a meaningful figure is their local relation to neighbors and their directional and temporal coherence when the dots are moving.[43] To wire an imagined superbrain that would recognize all possible dot combinations as distinct with equal ease would require a galactic number of connections and extensive computation. The real brain, however, is a "compromise" between its evolutionary "goals" and wiring/metabolic costs—an adaptation of brain circuits for making predictions and inferences about the physical world. For example, in nocturnal bats, a large portion of neurons and cortical connectivity is devoted to echolocation because echolocation is vital for their survival. Rodents with large sensory whiskers on their face developed a proportionally detailed somatosensory cortex with a remarkably precise topography of the snout whiskers.[44] In the predominantly visual primate, almost half of the neocortical neurons and wiring are allocated to the representation of the pictorial world. Finally, in the most complex brains, a large portion of the cortical mantle, called the associational cortex, is devoted to generating and processing events that are not directly related to sensory inputs or motor outputs. Remarkably, the cortical modules in the associational areas are not fundamentally different from the sensory or motor cortical areas, an indication that local computation in cortical modules is quite similar. Organizing most connections locally in cortical modules enables the brain to map out the neighborhood relations of the environment efficiently, because local interactions are the main organizational principle of the physical

40. See Cowey (1979) and Allman (1999).

41. Most maps are "distorted," however, such that certain peripheral parts, e.g., the mouth area in somatosensation and the fovea in vision, are represented by much larger cortical areas than are others. Allman (1999) is an excellent informative read on this subject.

42. For a quantitative treatment of wire optimization in the brain, see Cherniak (1995) and Chklovskii and Koulakov (2004).

43. Julesz (1995) is a marvelous account of the early stages of visual processing, with numerous illustrations of motion coherence of random dot patterns.

44. Read the original paper by Woolsey and Van der Loos (1970) or a recent review by Fox (2002) on the modular (barrel) organization of the somatosensory cortex.

world. We may conclude, therefore, that the statistically correlated features of the environment are the principal reason for the primarily local tensegrity organization of the neocortex.

In light of such anatomical–functional organization, it is surprising that in most visual experiments simple moving bars and gratings are most frequently used as stimuli. These shapes have high contrast and sharp edges, yet the surprising and consistent finding is that bars and gratings evoke neuronal patterns that are quite different from those elicited by natural scenes. The more robust responses evoked by natural scenes are often used as an argument in favor of some cognitive interpretation of the visual input. Of course, nothing prevents the observer from interpreting even a random dot pattern as a meaningful figure. The brain always interprets. This compulsive interpretation is the basis the Rorschach inkblot test used by clinical psychologists.[45] However, one may wonder why a monkey raised in captivity or an anesthetized cat would attribute some special significance to the snow-covered peaks of the Rockies or a Lotus parked in front of the Monte Carlo Casino. An alternative reason for the superior effectiveness of these natural stimuli is that the spatial statistics of their feature "neighborhoodness" are matched best by the connection topography and local computations of visual cortical neurons.[46] In natural scenes, neighboring elements tend to have high spatial and temporal correlations. Accordingly, the temporal response dynamics of the neurons in the visual cortex closely reflect the statistical properties of the visual scenes.[47] In general, the distributions of connections are "tuned" to extract the most likely information from the environment. The small cost we pay for such imperfection is illusions[48] that inevitably arise when the brain is occasionally confronted with an unusually low-probability geometry of stimuli.

The robust tensegrity plan prevents propagation of faults and allows no weak points. On the other hand, any compromise in the accuracy of the general plan has serious consequences. Allowing for just 10 percent imprecision could lead to the collapse of the tensegrity structure of the Superdome. Brain function fares no better. Suppose that we scramble the neurons a bit so that the new allocations will

45. The Rorschach inkblot test, developed by Hermann Rorschach, is a projective test of personality in which a subject's interpretations of 10 standard abstract designs are analyzed to evaluate the subject's emotional and intellectual capacities. The brain cannot help but interpret any input, be it fractals or random dots. Unfortunately, the inkblot test strongly depends on the subjective evaluation by the experimenter and is not any more reliable than interpreting dreams.

46. Fractal structure in the second-order statistics is ubiquitous for natural scenes (Ruderman and Bialek, 1994; Bell and Sejnowski, 1997). Neurons in the retina (Victor, 1999), lateral geniculate (Dan et al., 1996), and primary visual cortex V1 (Olshausen and Field, 1996; Yu et al., 2005) respond sparsely and most effectively in response to images with $1/f$ statistics (see Cycle 5 for explanation of this term).

47. In the study by Fiser et al. (2004), neurons in the ferret visual cortex responded in a much more coherent manner to a movie containing natural scenes than to a random-noise movie (see also Weliky et al., 2003).

48. What we see with our brain is much more (or less) than what meets the eye. Illusion is a perceived image that is deceptive or misleading. E.g., the moon seems larger in angular size when it is near the horizon than when it is high in the sky.

require a 10 percent increase in local connectivity. After rearrangement, we would still have the exact same connections among the neurons and the same representation of the physical world by the same neurons. However, carrying electrical pulses over longer distances would increase the metabolic costs and demand an enlarged vascular infrastructure. Most important, the coordination of brain oscillators and information transfer in multiple synaptic pathways would be substantially affected because of the cumulative temporal delays. Even with such a seemingly insignificant increase in wiring, we would lose all tennis games and could not articulate properly or perceive normally, as is often the case in people suffering from multiple sclerosis, a disease affecting the myelin insulation of axons.[49] Local communication is therefore the most robust program in the neocortex, allowing for the topographic representation of the internal and surrounding environments.

However, with only adjacent connectivity, no matter how dense, the cerebral cortex would not be a very useful device to guide the organism, because isolated local decisions are not enough for most complex brain operations. Global, collective decisions are needed for most cortical functions. Collective decisions, however, require the cooperative actions of both neighboring and distant areas. Such flexible cooperation among local and distant cell assemblies is believed to underlie nearly all cognitive behaviors.

Are a Thousand Mouse Brains Worth the Brain of a Human?

The answer is a definite "no" when it applies to the cerebral cortex. The fundamental reason is that simply placing more modules next to each other will not cause a novel performance to emerge. What makes the tensegrity plan so robust for a geodesic dome is that local static errors and construction weaknesses do not propagate. But locally confined connectivity is a major disadvantage for numerous computing tasks because with growth the newly added modules will be more and more distant from each other, making global communication progressively more difficult, for reasons I address later.[50] For now, it is enough to say that, with local connectivity only, propagating information from one part of the cortex to another may take too much time. To communicate with all cortical modules efficiently, the synaptic network diameter of the brain, that is, the average synaptic path

49. Multiple sclerosis (referring to microscopic scars) is the result of damage to myelin, the protective sheath surrounding nerve fibers of the central nervous system. When myelin is damaged, it slows down the speed of action potential propagation along the axons. See Keegan and Noseworth (2002) for a review.

50. Several brain structures follow a true tensegrity organization with mostly local connections (e.g., cerebellum and basal ganglia). These structures perform mainly parallel rather than global computation (see Cycle 13). Global computation and small-world-like organization of the neocortex are fundamental innovations of the mammalian evolution.

length from one cortical neuron to any other, should remain constant so that activity can jump from any place to some other place with more or less equal ease.

This point is where the information discussed above in connection with the "small-world" and "scale-free" networks becomes useful. To keep the synaptic path length constant, volume-demanding intermediate- and long-range connections are needed. A prerequisite for growth with preserved global connectivity is that single neurons should have longer axons as well as larger, more bushy dendritic trees with increasing numbers of spines to accommodate more connections. The diameter of the dendritic arbor of the large pyramidal neurons grew from approximately 0.2 millimeters in the mouse to 1 millimeter in the human cortex. The immediate consequence of the enlarged dendritic tree in larger brains is an increase of the mutual overlap of the nearby cells. A cylinder corresponding to the diameter of the dendritic tree of a single layer 5 pyramidal cell in the mouse and human contains approximately 3,000 and 100,000 neuronal cell bodies, respectively. Larger cells occupy more volume and require longer axons to connect them. As a result, the density of axons and dendrites per volume, and therefore the number of synapses per cubic millimeter, remains remarkably constant in different species.[51] This constancy explains why the submicroscopic structure of the cortex looks so similar in small and large brains. Because of this dense overlap, an afferent fiber shooting toward the surface in a straight line next to the cell body of a chosen neuron has, in principle, the same probability of contacting spines of that neuron as of any other neuron. This junglelike arborization of dendrites is the main reason why some investigators believe that afferents find their targets randomly. Others believe in specific patterns of innervation or "motifs" that follow precise hardwiring plans, like plumbing and electrical wiring in a building.[52] Because connection matrices governed by power laws provide a much richer and more diversified network than random choice or specific motifs, it is quite possible that the brain chooses to follow a power law design or some other formula even at the microscopic level.

Are small and large brains equally well connected? Keeping the synaptic path length constant while the brain grows is a necessary requirement for maintaining global communication among neurons and modules. Adding more than the bare minimum number of connections is, of course, advantageous for performance because additional connections allow more effective communication. A clear indication of a larger, more complex brain's "need" for long-range connections is that the volume of white matter increases at approximately at 4/3 power of the volume of gray matter during the course of evolution. In other words, the cerebral cortex of larger brains tends to have disproportionately more long-range connections than do brains of small animals (figure 2.5).[53] While in small insectivores the

51. Braak and Braak (1976) and Braitenberg and Schütz (1998).

52. Braitenberg and Schütz (1998) and Abeles (1982) suggest random connections. Ikegaya et al. (2004) emphasize extreme specificity. Wiring economists believe in mathematically defined laws (Chklovskii and Koulakov, 2004; Sporns et al., 2004).

53. Diameter and even volume of the brain are gross measures, however, because they do not faithfully reflect anatomical connectivity. E.g., the brain diameter of the giraffe is similar to that of the human brain, yet its long-range connections are much poorer.

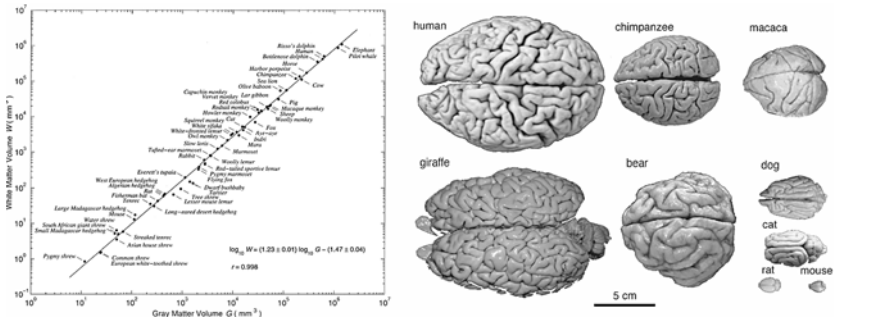

Figure 2.5. The cerebral cortex of more complex brains deploys disproportionately more axonal connections than does that of brains of small animals. Left: Cortical white and gray matter volumes of various species are related by a power law that spans five to six orders of magnitude. Connectedness is more important than size. Reprinted, with permission, from Zhang and Sejnowski (2000). Right: Despite the large variation in brain size, the periods of various network oscillations in the cerebral cortex are remarkably well preserved across mammalian species. Photos courtesy of Javier de Felipe.

white matter occupies only 6 percent of neocortical volume, it exceeds 40 percent in humans.[54] Furthermore, not all areas and connections expand proportionally. For example, while the primary visual areas only double in size from macaques to humans, the growth of the parietal and frontal cortical areas is 10–40 times larger in humans. The growth patterns in primary sensory areas may follow the small-world network recipe, since these areas deal with the statistical regularities of the outside world, a task that is similar in all mammalian species. On the other hand, in the proliferating "human-specific" associational areas, the needs and rules are unknown. More connections, at the expense of brain volume enlargement and maintenance costs, can provide more efficient computation.

The connectivity problem concerns not only the numbers of fibers but also communication speed. Conduction velocity of myelinated axons is linearly related to axon diameter, whereas that of nonmyelinated axons is proportional to the square root of the diameter. On the basis of increased anatomical segregation due to the various conduction delay lines, one expects increased separation of function, as well. Interhemispheric communication through thin callosal fibers less than 1 micrometer in diameter may lead to delays of more than 25 milliseconds.[55] The neocortical white matter consists of axons that span a vast spectrum of diameters, and the distribution of axon calibers may vary considerably in

54. For specific numbers, consult Tomasch (1954), Bishop and Smith (1964), and Swadlow (2000). The 4/3 power law was described by Allman (1999) and Zhang and Sejnowski (2000). At a single-cell level, axon arbors of cortical neurons also show scale-free (fractal) statistics (Binzegger et al., 2005), although dendrites may have more complex organizations (Cannon et al., 1999).

55. Ringo et al. (1994) speculate that this communication disadvantage has contributed to hemispheric specialization in animals with large brains. Indeed, unihemispheric sleep has been described in five species of cetaceans with very large brains (Lyamin et al., 2002).

different animal species. In the human brain, approximately 100–200 million axon collaterals serve to interconnect symmetric and asymmetric neuronal groups in the two hemispheres, forming the corpus callosum (or rigid body), and somewhat larger numbers of intermediate- and long-range fibers connect areas within the same hemispheres. This may sound like a lot of wires, but remember that there may be 20 billion neurons in the neocortex. Long-range connections thus may represent a minuscule fraction of neuronal connectivity.[56] Because of their scarcity, the "band width" of communication, that is, the amount of information transmittable per unit time, is seriously limited in these long-range connections. To compensate for the long distances they cover, the traveling velocity of action potentials is accelerated by their strong myelination. Myelin insulation not only speeds up spike transmission velocity but also protects axons from conduction failure, reduces the cross-talk from neighboring axons, and allows for transmission of much higher frequency pulses per unit time than thinner, unmyelinated fibers.

Conduction velocities vary 100-fold in the long-range connections from as slow as 0.3 meter per second in the very thin (0.1–0.5 micrometer) unmyelinated majority to an exceptionally fast 50 meters per second in thick myelinated axons that interconnect primary sensory areas. A small fraction of the myelinated fibers in the human brain can have as large as 5 micrometers of diameter.[57] Wrapping the axons with a thick insulation layer for rapid communication occurs, of course, at the expense of valuable space. The fastest conducting, large-diameter fibers may occupy 10,000 times the volume of the finest unmyelinated fibers of the same length, and they are limited to connecting primary sensory and action areas that require speed and short time-scale synchrony. Thus, unlike in the translationally invariant abstract small-world models, the expensive long-range connections in the brain must be used sparingly.

Corticocortical connectivity has changed with each turn of evolutionary differentiation, from the pallium of birds to a localized dense connectivity combined with precisely directed long-range connections in primates. Although brain size and long-range connectivity often go hand in hand, there are some notable exceptions. For example, the corpus callosum is a phylogenetically recent structure, present only in placental mammals. We can hypothesize, therefore, that the brains of placental mammals may be more capable of global communication than are those of marsupials and monotremes with similarly

56. See Schütz and Braitenberg (2002). Axon collaterals of many neurons in the neocortex remain local (e.g., the numerous spiny stellate cells of layer 4 and most inhibitory interneurons). Since the many different types of neurons are not equal nodes in the mathematical sense, a coalition of local neurons may be regarded as a functional unit. If calculated this way, the proportion of long-range fibers may increase more than the minimum requirement predicted from the strict small-world or scale-free network rules.

57. Most intermediate- and long-range corticocortical projections originate from layer 2 and layer 3 pyramidal cells. It is not clear whether the large-caliber variation represents fibers of these neurons or, alternatively, if very large-caliber axons arise from hitherto unidentified neurons or inhibitory interneurons.

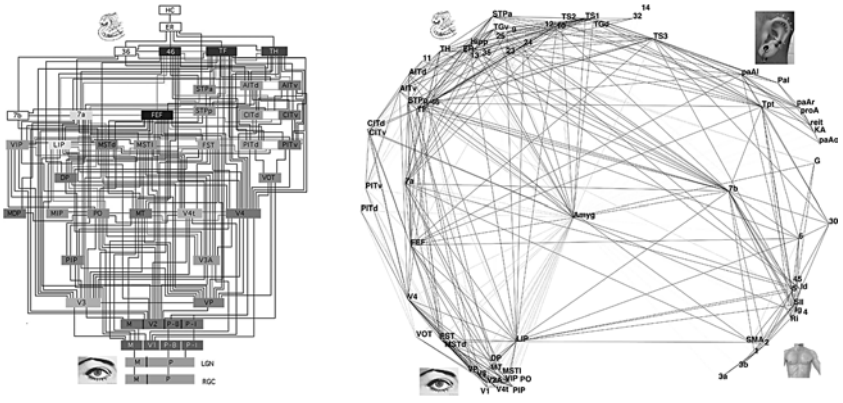

Figure 2.6. Hierarchical and looplike organization of brain systems. Left: Multiple processing stages and numerous multiple-loop connections of the visual system from the eye to higher order associational cortices. Reprinted, with permission, from Felleman and Van Essen, (1991). Right: Spatial segregation of systems (e.g., visual, auditory, somatosensation, associational) on the basis of connectivity. Note high clusters of connections within respective systems. Reprinted, with permission, from Young (1992).

sized brains, because of their more efficient global connectivity.[58] Long-range connections within the same hemispheres also follow some wire-optimization rule. Fibers connecting different cortical areas form macroscopic bundles that are orderly arranged so that intermediate connections can depart easily from the bundle, like cables in old telephone switch centers. David Van Essen and his post-doctoral fellow Daniel Felleman at Washington University–St. Louis, showed that the 30 or so cortical domains involved in processing visual information are connected by at least 300 relatively distinct intermediate and longer connections, implying a hierarchical organization (figure 2.6). Again, this arrangement is not by chance. Hierarchical structure is an inevitable consequence of complexity because complex systems represent multiple nested levels of organization.[59]

Primary sensory cortical areas are relatively far from each other in the cerebral cortex and have no direct connections between them, but they are linked indirectly by the higher order cortical areas sandwiched between them. Connection probability has long been used in attempts to define functionally meaningful anatomical areas and systems, such as primary sensory areas, motor areas, higher order associational areas, sensory and motor systems, the memory system, and

58. Marsupials and monotremes have a large anterior commissure, however. Not much work has been done on the hemispheric specialization or the intrahemispheric long-range connections in these creatures.

59. Salthe (1985) is an excellent introduction to hierarchy theory, levels of organization and problems of scaling.

others.[60] By examining many alternative arrangements of 11 distinct cortical areas in the macaque frontal lobe, Charles Stevens at the Salk Institute in La Jolla, California, has found that the arrangement that is actually present in the brain minimizes the volume of the axons required for interconnecting the areas. These examples illustrate that the cerebral cortex is a highly ordered network at the macroscopic scale.[61] Topographic arrangement is an economic way to optimize component placement to reduce excessive wiring and minimize axon conduction delays. Efficient computation depends on fast temporal solutions, and it is possible that such temporal advantages "drive" optimal brain wiring.

Complexity of Wiring in the Neocortex

The combination of the robust local tensegrity design and functionally relevant long-range corticocortical pathways provides an economic solution for establishing functionally effective paths across the vast domains of the neocortex. The small-world-like organization of the neocortex, as opposed to strictly local, random, or all-to-all connectivity, provides a higher order of wiring complexity.[62] Moreover, areas of the neocortex in higher mammals are more strongly connected than needed to form a graph structure. Areas preferentially connected are referred to as cortical systems. If we regard the brain as a complex system, we rightfully expect that its intricate connectivity has a lot to do with its complex operations. But what is complexity?

Complexity is not just complicated stuff but a unique quality that emerges from the relationship or interaction among elements. Think about a good wine.

60. Axonal connections have long been used by neurologists to identify the localization of neurological symptoms, especially before the imaging era. Mesulam (1998) is a thorough review of the relationship between traditionally defined systems and alleged functions in primates.

61. Anatomical systems are defined by the strength of their interconnections rather than by spatial proximity. The monumental works of Felleman and Van Essen (1991) and Young (1992; Scannel et al., 1995) were among the first large-scale comparisons of systems connectivity. For the optimum placement of frontal cortical areas, see Klyachko and Stevens (2003). Axon length economy may explain the separation of dorsal ("where") and ventral ("what") visual pathways (Sporns et al., 2000a and b; Ungerleider and Mishkin, 1982). Young and Scannell (1996) criticize the "if connected then adjacent" wire economy rule (e.g., the retina and lateral geniculate are far from each other) and suggest that if any component placement rule exists, then it is this: if adjacent, then connected. However, neighborhood relations do not guarantee connectedness either (e.g., Alheid and Heimer, 1988; Léránth et al., 1992).

62. The claim that the brain is most sensitive to those environmental perturbations that match the statistics of its organization is related to Edelman's (1987) "neural Darwinism," which posits that evolution of cortical connectivity reflects an adaptation to the statistical structure of sensory inputs (Sporns et al., 2000a and b). Edelman and colleagues suggest that wiring economy is a "byproduct" of functional adaptation. Adaptation serves to maximize complexity by connecting neuronal groups according to the probability statistics of sensory inputs. Although identical anatomical connectivity of neurons can be achieved by various groupings, it appears that evolving wired systems always choose optimum component placements (Cherniak, 1995).

When you describe its bouquet, you refer to a blend of scents, richness, finesse, harmony, balance, and other fancy words that characterize a really good cabernet sauvignon. Analogously, the territory of complexity is somewhere halfway between chaos and order, stochastic and deterministic, random and predictable, labile and stable, homogeneous and nonhomogeneous, segregated and integrated, autonomous and dependent, unconstraint and fixed, chance and necessity, aggregation and differentiation, competition and cooperation, figure and background, context and content, anarchy and constraint, light and dark, matter and energy, good and evil, similar and different (figure 2.7).[63] Complex connectivity can be defined quantitatively using the same halfway logic: neither random nor regular, neither local nor fully connected, that is, a scale-free system that obeys a power law.[64] Complexity arises from the interaction of many parts, giving rise to difficulties in linear or reductionist analysis due to the nonlinearities generated by the interactions. Such nonlinear effects emerge from both positive (amplifying) and negative (damping) feedbacks, the key ingredients of complex systems. Typically, the relationships between elements in a complex system are short range, but because of the feedback loops, the imported information that passes through a local system is modified before being exported to other local or distant systems. So when it comes to organization rules, one has to address the issue of whether the rules are the same or different at the various levels, in our case, the whole cerebral cortex, cortical systems, and their subdivisions, because not all levels are engaged for particular tasks.

How far information travels is typically hard to define because the boundaries within and across complex systems are vague. Boundary decisions are usually based on the experimenter's methods and prejudices rather than on objectively defined properties. A case in point is the often-disputed borders between neocortical areas. Korbinian Brodmann often lamented about Santiago Ramón y Cajal's "erroneous" views on cortical lamination. Using sections stained with the method of Franz Nissl, Brodmann distinguished 47 areas in the human brain and compared them with those in a number of other mammals, including primates, rodents, and marsupials. Although his classification scheme remains the gold standard, several Brodmann areas have been further subdivided in recent years, due to the development of more sophisticated morphological criteria.[65] Among these new criteria,

63. My recommended source on complexity is Herbert Simon's landmark book on the empirical study of organizations (Simon, 1969; see also Kauffman, 1995). Kelso (1995) is perhaps the most user-friendly for psychologists and cognitive scientists. For a brief perspective on the subject, see Koch and Laurent (1999).

64. According to Bak (1996), complexity occurs only at one very special point: not where there is chaos or where there is trivial predictability but where there is a transition between these states with a $1/x$ distribution.

65. Brodmann's systematic studies on the human cerebral cortex appeared between 1903 and 1908 as a series of communications in the *Journal für Psychologie und Neurologie* (which lives on as the *Journal für Hirnforschung;* see Brodmann 1909/1994). Before Brodmann, confusion had reigned regarding the laminar structure of the cortex and the taxonomy of cortical areas. Small-brained animals have fewer areas defined by Nissl staining (e.g., the hedgehog has only 15), supporting the idea

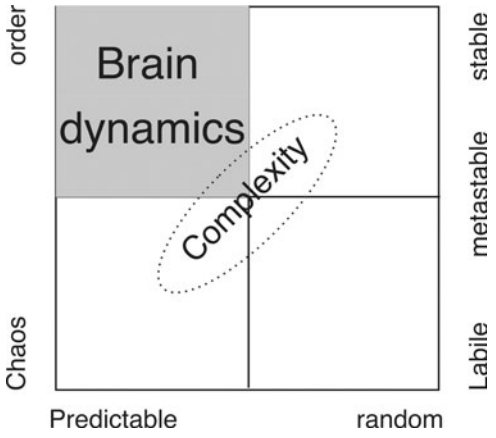

Figure 2.7. Complexity occupies the boundary between disorder (maximum entropy) and order. It is neither fully predictable nor fully random. Complex systems are governed by simple power laws. The dynamic range of the brain varies between complex and predictable.

connectedness appears to be the most decisive. There is no doubt that there are some variations in the fine cortical organization among the areas, but what appears to be the primary determinant of function in the cortex is how each area is related to other areas. Connectivity is of the essence.

Giulio Tononi, Olaf Sporns, and Gerald Edelman from the Neurosciences Institute in La Jolla, California, searched for a structure-based metric that could more objectively define "neuronal complexity" and capture the relationship between functional segregation and global integration of function in the brain. Using the concepts of statistical entropy and mutual information, they estimated the relative statistical independence of model systems with various connectivity structures. Not surprisingly, they found that statistical independence is low when system constituents are either completely independent (segregated) or completely dependent (integrated).[66] However, using their formal definition of complexity, they showed that statistical independence increased when segregated assemblies

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that encephalization is associated with increased cellular differentiation. Contemporary imaging methods use Jean Talairach's atlas (Talairach and Tournoux P, 1988). Each page in the atlas describes a slice of the human brain within a two-dimensional grid and refers to Brodmann numbers. The problem with anatomical classifications is not whether there are architecturally distinct areas but whether and how they reflect differential functions.

66. Tononi et al. (1994, 1996) estimated complexity, using the theory of stochastic processes and information theory. Entropy is a measure of the amount of disorder in a system. In information theory, it refers to the amount of randomness in a signal. The mutual information between two variables $I(x|y)$ is defined as the difference of entropy on x generated by the knowledge of y. The numerical value of

coexisted with some integration between them. Complexity reached a maximum when a large numbers of assemblies of varied sizes were combined. This feature, as described above, is the hallmark of scale-free systems, governed by power laws. In future Cycles, I refer to the small-world-like organization of the neocortex to indicate the lack of characteristic scales of medium- and long-range connectivity but with the implicit understanding that connections are much stronger among many cortical areas than would be needed by the simplest scale-free graph.

In a series of follow-up experiments mimicking Darwinian natural selection, Tononi and colleagues analyzed large numbers of graphs and found that what mattered most was not the mere number of connections present but the underlying connection patterns. Graph architectures ideally suited for maximum entropy (independence), integration (statistical dependence), and complexity were fundamentally different. Dynamics with high complexity were supported by architectures whose units ("neurons") were organized into densely linked local groups that were sparsely and reciprocally interconnected. These computational studies echo the economist Mark Granovetter's dictum about the strengths of weak ties.[67]

Unfortunately, one-dimensional abstract networks, used in these simulation studies, consist of identical nodes (neurons) and links (synapses) and lack temporal features such as conduction delays. In other words, they lack real-world dynamics that add further kinks to the complexity issue. Nevertheless, quantitative approaches such as those pioneered by Tononi, Sporns, and colleages, allow us to hypothesize about the information transfer in brains of various connection complexities. For example, if local groups are more strongly connected by long-range axons than expected from scale-free organization, this knowledge suggests more efficient global integration. Similarly, connectivity among neuronal groups and group aggregates can be used to define the boundaries at multiple spatial scales and to indicate potential functional operations at various spatial levels. In addition to connectivity, another approach for enhancing the complexity of a system is by introducing novel types of components. In the cortex, such component diversity is achieved by using different neuron types.

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the amount of information we cannot account for is entropy. With this "information definition" of complexity, the human mind enters the picture since information is not a physical thing. Similar ideas on complexity measures have been advocated by Stuart Kauffman, who suggested that the best strategy to identify complexity is to search at the phase transition between order and disorder, that is, at the edge of chaos (Kauffman, 1995). To some extent, Kauffman's system is based on Ilya Prigogine's nonequilibrium thermodynamics, which suggests that complex systems near equilibrium minimize their rate of entropy production (independence). The original seed of all these ideas is likely from Charles Darwin: order emerges from disorder without an outside agent, although many argue that the term "natural selection" assumes an external selective "force."

67. Granovetter (1973, 1995). The entropy-based definition of complexity is essentially the same as the power-law–dependent scale-free distribution of connections.

Excitatory Cortical Networks: An Oversimplified Perspective

A fundamental problem in studying the brain derives from the fact that it is organized at multiple spatial and temporal scales. Examining a single neuron, small circuit, or region in isolation is complicated by the difficulty that each of these levels is a complex function of its lower level constituents and, at the same time, is embedded in a large-scale organization. No wonder that it is still debated whether functional organization emerges from a pluripotent network with identical constituents in which connectivity rules or from a system of components each having a well-defined function. According to the simplest reductionist approach, one must understand the basic and common properties of all neurons, construct and examine the properties of a "canonical" cortical circuit,[68] and proceed from there by analyzing how inputs from the external sensors, such as the eyes and ears, affects function in such basic circuits. A popular framework, introduced by Moshe Abeles of the Hebrew University in Jerusalem, is a feedforward network or "synfire chain"[69] matrix of pyramidal cells across many hypothetical layers of identical neurons, where model layers may represent different anatomical layers of a single cortical column or brain areas of the neocortex. Although there are some specific examples of such unidirectional, feedforward connections in the brain, they are neither robust nor efficient for most functions performed by real cortical networks. First, errors propagate and accumulate without corrections in the multiple layers. Second, messages become too long while propagating across the different layers due to synaptic and conduction delays. Because true feedforward networks are hierarchical decision makers, top-down influences or global decisions that would emerge from the collective contribution of many constituents are left unexploited.[70] These shortcomings can be improved by recurrent or feedback excitatory connections within and between layers. Such recurrent networks can restore the original pattern from its fragmented versions.[71]

68. Such a simple unit consists of a pyramidal cell and a feedback inhibitory interneuron or some variation of such connectivity (Douglas and Martin, 1991, 2004).

69. Synfire chains of Abeles (1982) serve as a model of of cortical connectivity. The chains consist of group of neurons linked together in a feedforward manner so that a wave of activity can propagate from one end to the other, unidirectionally. More sophisticated synfire chains also include inhibitory interneurons and these balanced models are used to study spike synchrony propagation, for example from stimulus perception to initiating a behavioral output.

70. Hierarchy need not imply top-down relations of authority or an agent. The basic structure of matter is hierarchical, an inevitable consequence of self-organization. Before Simon (1969), hierarchy was regarded as a static structure. Simon's dynamic system was strongly influenced by "general systems theory," the topic introduced by the Hungarian writer and philosopher Arthur Koestler (1967) and developed further by Stanley (1985). According to these views, an organism is a self-regulated hierarchy. Due to competition, activity patterns become progressively more complex, flexible, and creative as we move up the hierarchy. These thoughts are the roots of the single-cell doctrine in neuroscience (Barlow, 1972).

71. Because of their pattern completion ability, recurrent networks are also known as "autoassociators" (Kanerva, 1988).

Although the cerebral cortex is made up primarily of pyramidal neurons, their intrinsic properties may show large enough variations to make a difference in their integration and transfer properties. Pyramidal cells in layers 2, 3, 5, and 6 and the spiny stellate (star-shaped) cells of layer 4 differ not only in terms of their connections but also by in their biophysical properties.[72] Axons of stellate cells remain local, whereas those of most pyramidal neurons project to distances larger than the size of the postulated neocortical modules. Axon collaterals of large motor cortex neurons reach the most distant end of the spinal cord. The five principal-cell categories in layers 2–6 release the same excitatory neurotransmitter, glutamate, in their axon terminals, so at one level they are quite similar. On the other hand, they are of different sizes and possess sufficiently different biophysical properties to postulate that they can give rise to at least five degrees of freedom in neocortical computation, in addition to connectivity.

The next organizational level above the neuron is the hypothetical cortical module. Most investigators emphasize how little the neocortex varies in its fundamental architectonic appearance from one cortical region to another, while acknowledging that cell size and density can vary systematically. This basic similarity implies that local computations at any cortical location are fundamentally the same.[73] Accordingly, the area differences in function in each area must emerge from the unique patterns of input and output connections. The precise connectivity among the various cell types is not fully known, although some general connection plan exists. Based on the assumption that the basic flow of information in the neocortex is from the direction of the external world to higher areas, ascending (feedforward) and descending (feedback) connections are distinguished. By and large, connections from one area to another are classified as ascending if they terminate mainly in layer 4, and descending if the terminals are distributed in layers other than layer 4. The density of intermediate- and long-range connections varies extensively among cortical areas, indicating that some interactions are more important than others by virtue of their degree of connectedness. Quite often, these connection patterns correlate nicely with other anatomical markers of regional cortical organization, but the many discrepancies remain the source of constant debate regarding the precise delineation of boundaries between cortical areas.[74]

The reductionistic conclusion that one would like to draw from the above discussion is that the same physiological function, such as vision and somatosensation,

72. Although they have a different name, the spiny stellate cells are essentially pyramidal cells without an apical dendritic shaft. Numerous dendrites originate from the cell bodies in all directions. This star-shaped appearance is the source of the distinguishing term "stellate." Their axons are dense locally and rarely leave the vicinity of the cortical module.

73. An excellent review in favor of the similarities of cortical modules is Zeki (1978).

74. The distinctly high density of layer 4 stellate cells in area 17 of the visual cortex of the primate and the large Betz cells of motor area 4 are examples of dramatic architectonical differences. Analyzing 834 connections between 72 cortical structures in the macaque cortex, Young and colleagues (Young, 1992; Young and Scannel, 1996; 2000) have shown "hubs" with high connection densities, corresponding roughly to visual, auditory, somatosensory, and frontolimbic areas, with ordered

in mammalian brains of different sizes is supported by similar circuits, composed of the same neuron types. Unique functions arise not (only) from the unique local organization but from the unique embeddedness and connections of the local networks to other networks. Rapid growth of neocortical neuron numbers is possible because disproportionately fewer long-range connections are needed in large brains to assure the same degree of effective connectivity as in small brains. The hope, then, is that the quantitatively different architectures in different brain areas and species have some mathematically predictable relationship, a profoundly important message because it is an important justification of research on the brains of small animals in a quest to understand our own. If we come to understand the mysteries of basic cortical anatomical organization and the interactions of cortical areas in rodents, then the generated knowledge should be applicable to the human cortex, as well. Some small surprises may emerge, however. Esther Nimchinsky and Patrik Hof at Mount Sinai University in New York and John Allman at the California Institute of Technology have recently described a unique population of unusually large, spindle-shaped neurons in layer 5 of the insular and anterior cingulate cortex of humans and great apes but not in other mammals.[75] However, it remains to be seen whether they are qualitatively different from other layer 5 neurons, possessing some uniquely extensive connections or biophysical properties.

So far, I have discussed only the connectivity of the principal, excitatory cell types of the neocortex. No matter how well connected these neurons are, in themselves they are not capable of carrying out anything useful. A major problem that we face is that excitation spreads in all directions without any mechanisms to curb the spread of activity. Without a proper control system, principal-cell types connected by random, small-world, or any kind of network design would simply behave like autonomous avalanches, building up very large excitation over an ever-expanding territory and then shutting off from exhaustion. In order to generate the harmony of tensegrity in cortical circuits, excitation must be balanced with an equally effective inhibition. In the cortex, the solution is a stabilizing negative feedback control, provided by the inhibitory interneuron system, which I discuss in Cycle 3.

Briefly . . .

The neocortex is built from a multitude of five principal-cell types and numerous classes of interneurons. Early formulation of cortical structure emphasized the

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degrees of connectivity between areas defined by Brodmann. On the other hand, recent proposals on the internal connectivity of the visual system bear little resemblance to the classical Brodmann maps (Felleman and Van Essen, 1991). An extensive summary of the corticocortical connections in the rhesus monkey is presented in Schahmann and Padya (2006). For a short but illuminating discussion about local architecture and global connectivity, see Kaas (2000).

75. Nimchinsky et al. (1999). Similarly large neurons (Betz cells) in the primary motor cortex of hominids have been known for some time. The potential significance of these giant "spindle-shaped" neurons is discussed in Allman (1999).

modularity of the neocortex, for example, juxtaposed cortical columns in large numbers. Its robust local tensegrity organization has allowed continuous growth from the small brain of a tree shrew to the giant brain of the whale. Medium- and long-range connections that compose the white matter and interconnect non-adjacent cortical neuronal circuits are relatively sparse but sufficient to provide the indispensable conduit for keeping the synaptic path lengths constant in brains of different sizes. Such interconnectedness of cortical areas is a prerequisite for global operations in finite temporal windows. The precise connectivity among the various principal-cell types is not fully known, although some general connection plan exists. There is a consensus among neuroscientists that the principal-cell types and their basic connectivity have been well preserved from the smallest to the largest brains. The small-world-like, scale-free organization of cortical architecture may provide some quantitative rules for the growths of both cell numbers and associated axonal connections while minimizing the cost of connectivity. However, the available anatomical data indicate that cortical areas processing similar kinds of information are more strongly connected than required by a simple random graph. These preferentially connected areas form the motor, visual, auditory, somatosensory, gustatory, olfactory, and higher order cortical systems. However, with excitatory connections only, no computation is possible because any input would simply recruit all neurons of the cortex into unstructured population bursts. Limiting excitatory spread and segregation of computation are solved by balanced interactions between the excitatory principal cells and inhibitory interneurons.

Cycle 3

Diversity of Cortical Functions Is Provided by Inhibition

> Nothing in biology makes sense except in the light of evolution.
>
> —Theodosius Dobzhansky

According to classical statistical thermodynamics, there is only one kind of interaction between the elements: excitation (collision). This can lead to changes in only one direction. Brains are different. Brains use not only excitation and but also inhibition in their normal operations. This additional component is responsible for the fundamental difference between disorder-destined physical systems and the order-centered brain dynamics.

As described at the conclusion of Cycle 2, the excitatory networks of the cerebral cortex are inherently unstable. Tensegrity dynamics can be maintained only if the excitatory effects are balanced by equally effective inhibitory forces, provided by specialized inhibitory neurons. If only excitatory cells were present in the brain, neurons could not create form or order or secure some autonomy for themselves. Principal cells can do only one thing: excite each other. In the absence of inhibition, any external input, weak or strong, would generate more or less the same one-way pattern, an avalanche of excitation involving the whole population.[1]

1. Abstract neural network models are different from their real-world counterparts. E.g., Hopfield nets are built from a large number of simple equivalent components ("neurons") and the computational properties emerge as collective properties. However, there is no real excitation in the Hopfield net, just 0 and 1 logical states (Hopfield, 1982). In later models, components have graded responses but no inhibition (Hopfield and Tank, 1986).

However, the brain is a system with diversified components, where different types of neurons are related in a particular way to achieve unity of a particular kind. In this Cycle, I first provide a brief overview of the types of cortical interneurons and their connections with each other and with the principal excitatory cells and discuss how the excitatory and inhibitory forces balance each other through oscillations.

Inhibitory Networks Generate Nonlinear Effects

Propagation of activity in excitatory networks is simple and predictable. Excitation just generates further excitation, independent of time, wiring complexity, strength of excitation, or, in fact, any other factor. Positive forces can move the system only in a forward direction. An excitatory network always converges toward the same irreversible end despite the different magnitudes or forms of starting conditions. Inhibitory networks are fundamentally different. To illustrate this difference, compare chains of excitatory and inhibitory neurons (figure 3.1). Independent of the details, the evolution of activity in the purely excitatory network is monotonic excitation. Excitatory neurons connected in series excite each other at every step, resulting in a chain reaction of ever-increasing activity without global stability. In contrast, when an inhibitory interneuron at the beginning of the chain is activated, it will suppress the activity of its target neuron. As a result, the third interneuron in the chain will be less suppressed by the second interneuron, so the activity of the third neuron may increase. Neurophysiologists refer to this process

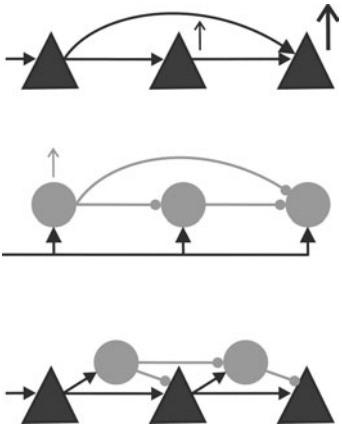

Figure 3.1. Inhibition introduces "hard-to-predict" nonlinearity in cortical circuits. Excitatory chains (black) produce only monotonically increasing excitation. In contrast, in inhibitory (gray) and mixed circuits, the spread of activity can be strongly modified, and the ultimate outcome depends on the fine details of connections and synaptic strengths (arrow, excitatory; circle, inhibitory). Vertical arrows indicate the magnitude of activity.

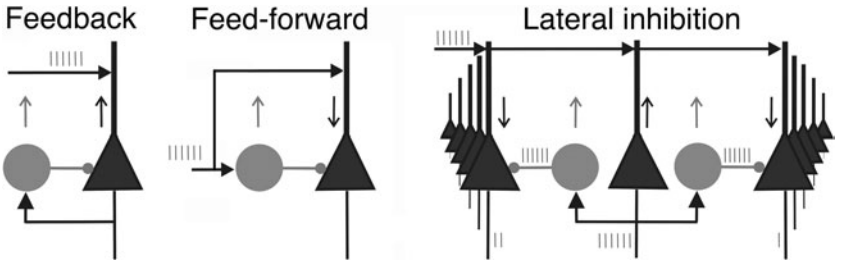

Figure 3.2. Negative (inhibitory) feedback provides stability. Feedforward inhibition dampens ("filters") the effect of afferent excitation. Lateral inhibition provides autonomy (segregation) of neurons by suppressing the similarly activated neighboring neurons ("winner take all").

as disinhibition. The disinhibited third neuron, in turn, will suppress its own downstream target, and so on. Now consider a ring of excitatory neurons with one or more inhibitory interneurons embedded in the circuit. Input activation brings about both spreading excitation and inhibition. The firing patterns of the individual neurons in the ring are hard to predict because their activity strongly depends on the exact details of the connections. A minor change in some of the parameters can result in dramatic changes in the firing properties of all partners involved. This property is known as nonlinearity.

Networks built from both excitatory and inhibitory elements can self-organize and generate complex properties.[2] However, even in the simplest partnership of a principal cell and interneuron, the pattern of firing depends on the details of wiring (figure 3.2).[3] In a recurrent inhibitory circuit, increased firing of the principal cell elevates the interneuron's discharge frequency, and the interneuron, in turn, may decrease the principal cell's output, similar to the action of a thermostat. Stabilization by negative feedback typically comes in the form of various oscillations (discussed in Cycle 6). In a feedforward inhibitory configuration, increased discharge of the interneuron, as the primary event, results in decreased activity of the principal cell. Such simple pairing of excitation and inhibition can increase the temporal precision of firing substantially. This is because depolarization of the principal cell, initiated by the excitatory input, is reduced quickly by the repolarizing effect of feedforward inhibition, narrowing the temporal window of discharge probability. Fast coupling of the excitatory and inhibitory influences can bring about submillisecond precision of spike timing.[4]

Any departure from the simple feedback or feedforward partnership inevitably

2. Systems with multiple nested structures are called hierarchies. The cortex with its rich variety of neuron types and multiple organization levels is a complex hierarchical system.

3. Shortly after the discovery of feedforward inhibition in the cortex (Buzsáki and Eidelberg, 1981, 1982; Alger and Nicoll, 1982), the fundamental neurophysiological differences between feedback and feedforward inhibition were emphasized (Buzsáki, 1984; see also Swadlow, 2002).

4. Pouille and Scanziani (2001).

increases the complexity of the firing patterns of the participating cells. For example, when two interneurons are activated simultaneously, their combined effect on the target principal cell depends primarily on the interaction between the interneurons. Inhibition, as a "negative force," introduces nonlinear, hard to predict effects. An extension of feedback inhibition is lateral inhibition. This occurs when activation of a principal cell recruits an interneuron, which in turn suppresses the activity of the surrounding principal cells. Suppose that two principal cells are excited by the same input, but the input to principal cell A is slightly stronger than the input to principal cell B. If neuron A and B share a common inhibitory interneuron, the gain in neuron A results in a suppression of neuron B's activity. The same outcome occurs if the input strengths to neurons A and B are equal but the synapse between neuron A and the interneuron is slightly stronger than that between neuron B and the interneuron. The initial minor difference in the inputs results in a very large difference in the output of the two neurons. The same asymmetry can be produced if input to neuron A arrives slightly earlier than the input to neuron B. This increased autonomy by competition is also known as "winner-take-all" mechanism, a nonlinear selection or segregation mechanism.

Speaking more generally, cortical networks gain their nonlinearity and functional complexity primarily from the inhibitory interneuron system.[5] Such complex interactions between the excitatory and inhibitory neuron pools have at least two useful consequences. First, principal cells will neither be trapped in repeated excitatory avalanches nor become completely suppressed, unable of responding to inputs. Instead, in real networks the set point is somewhere in the middle, so principal cells embedded in cortical networks are able to react robustly, when needed, even to the weakest physiological input. In physics, such critical state is referred to as phase transition, because external forces can shift the system in either direction. A textbook example of a state transition is the shift between water and ice. A slight change in temperature (an externally imposed influence) can shift the state in either direction. If a system, for example, a neural network, can self-organize in such a way as to maintain itself near the phase transition, it can stay in this "sensitized" or metastable state until perturbed.[6] Despite being maximally sensitized to external perturbations, neuronal networks with multiple levels of excitatory and inhibitory constituents are resilient systems, capable of absorbing large external effects without undergoing functional breakdown.

Another fundamental service of the inhibitory system is that it provides a high degree of autonomy for individual principal cells or cell groups. Cooperation of interneurons in the same "class" (see discussion on diverse classes below) can secure the spatiotemporal segregation of principal cells to perform a

5. Another important source of nonlinearity is derived from the numerous subcortical modulatory neurotransmitters (Steriade and Buzsáki, 1990; McCormick et al., 1993). Part of the subcortical effect is mediated by cortical interneurons (Freund, 2003).

6. An oft-used term for such maintained phase transition is "self-organized criticality" in physics. Per Bak's fascinating book on self-organized criticality (Bak, 1996) links self-organization to cascading failures. For criticism of his treatment of the topic, see Jensen (1998).

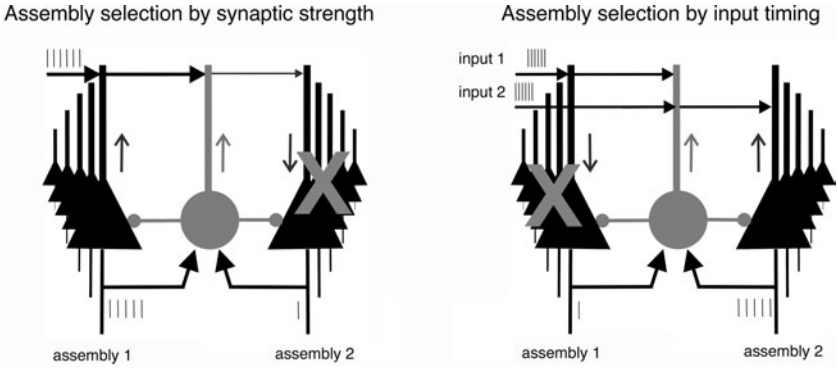

Figure 3.3. Inhibition is essential for cell assembly selection. Slight differences in synaptic strengths between the afferent input and neurons in assembly 1 and 2 can completely silence the competing assembly. In case of equal input strengths, the earlier input selects the assembly and silences the competing assembly by feedforward and lateral inhibition.

given function. As discussed repeatedly in subsequent Cycles, the most basic functions accomplished by neuronal networks are pattern completion and pattern separation, functions related to the concepts of integration and differentiation. Separation of inputs in a network with only excitatory connections is not possible. However, with inhibitory connections, the competing cell assemblies and even neighboring excitatory neurons can be functionally isolated, and excitatory paths can be rerouted by the traffic-controlling ability of coordinated interneuron groups. The specific firing patterns of principal cells in a network thus depend on the temporal and spatial distribution of inhibition. As a result, in response to the same input, the same network can produce different output patterns at different times, depending on the state of inhibition (figure 3.3). The coordinated inhibition ensures that excitatory activity recruits the right numbers of neurons in the right temporal window and that excitation spreads in the right direction. None of these important features can be achieved by principal cells alone.

Interneurons Multiply the Computational Ability of Principal Cells

The term "cortical interneuron" dates back to times when inhibitory neurons were thought to provide only somatic feedback inhibition onto local pyramidal cells. Because their short-range connections were alleged to be the rule, an alternative term "local circuit interneuron" was also in use for a while. Some interneurons, however, do project as far as principal cells. Nevertheless, the term "cortical interneuron" has been preserved with extended roles, much like the now divisible atom in physics (Greek *a-tom*, cannot be cut further). Because all known cortical

interneurons, which make up less than one-fifth of the cortical neuronal population, release the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), the term "inhibitory interneuron" unambiguously defines the inhibitory cell population in the cerebral cortex.

How can such a minority group keep in check the excitatory effects brought about by the majority principal cells in cortical networks? Interneurons deploy numerous mechanisms to meet this challenge. In contrast to the typically weak synaptic connections between principal cells, principal cell–interneuron connections are strong. In the return direction, a typical interneuron innervates a principal cell with 5–15 synaptic terminals (or boutons). Furthermore, almost half of the inhibitory terminals are placed at strategically critical positions for controlling action potential output. On the axon initial segment and cell body of principal cells, there are only inhibitory synapses supplied by several chandelier and basket interneurons. The threshold for action potential generation is much lower in interneurons, and often a single action potential of a presynaptic principal cell is sufficient to discharge an interneuron, as Jozsef Csicsvari, a graduate student in my laboratory, has shown.[7] As a result, basket and chandelier interneurons work harder, and their overall firing rate is several times higher than that of the principal cells, such that the total number of inhibitory postsynaptic potentials (IPSPs) per unit time, impinging upon a typical principal cell, approximately matches the effects of the excitatory postsynaptic potentials (EPSPs).[8]

However, both the kinetics and the spatial distribution of IPSPs and EPSPs are remarkably different. The rise time and decay time of IPSPs are much faster, and their amplitude is larger than those of EPSPs. This faster kinetics is the main reason why interneurons are so much more efficient in timing the action potentials of pyramidal neurons than are excitatory inputs from other pyramidal cells. Excitatory potentials dominate the dendrites of principal cells, whereas only IPSPs impinge upon the cell body (soma) (figure 3.4). The result of this arrangement is reflected by the larger power of high-frequency currents in the extracellular space in the somatic layers (where the cell bodies concentrate), relative to the dendritic layers (to where most excitatory inputs arrive).

It is through the opposing forces of excitation by principal cells and inhibition by interneurons that the tensegrity harmony of cortical activity is established. This balanced partnership ensures an overall homeostatic regulation of global firing rates of neurons over extended territories of the cortex and at the same time allows for dramatic increases of local excitability in short time windows, necessary for sending messages and modifying network connections. Balance and feedback

7. See Csicsvari et al. (1998). Gulyás et al. (1993b) provides electron microscopic evidence that excitatory postsynaptic potentials (EPSPs) in interneurons can be reliably evoked by single presynaptic spikes through just a single release site; see Barthó et al. (2004) and Silberberg et al. (2004) for related observations in the neocortex.

8. In addition to spike-related release of GABA, the inhibitory neurotransmitter is also released "spontaneously" in the absence of presynaptic action potential. The exact functional role of these tiny inhibitory currents (dubbed as "minis") is not well understood, but they may contribute to the stability of cortical networks (Nusser and Mody, 2002; Mody and Pearce, 2004).

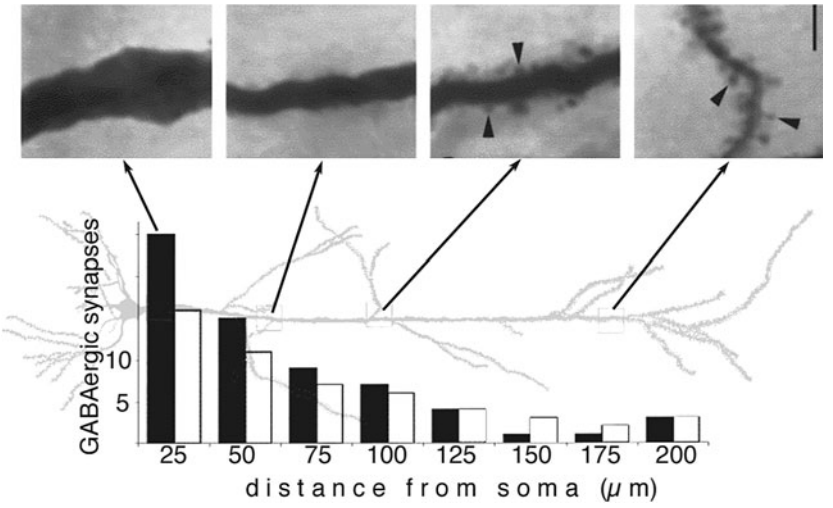

Figure 3.4. The perisomatic (output) region of pyramidal cells is fully controlled by GABAergic inhibition. The proportion of GABAergic synapses decreases, whereas the number of spines (associated mainly with excitatory synapses) increases as a function of distance from the soma. Modified, with permission, from Papp et al. (2001).

control are also essential principles for oscillations, and interneuron networks are the backbone of many brain oscillators.

In Cycle 2, I mentioned that the five main principal-cell types have distinct functional properties. This distinctness results from the unique combination of ion channels in the membrane and from their morphological individuality. Zachary Mainen and Terry Sejnowski at the Salk Institute have shown that the biophysical behavior of their computer-model neurons could be changed dramatically by altering their morphology.[9] For example, a neuron with a large or small dendritic arbor and neurons with similar geometry but different distribution of ion channels will generate a different output in response to the same input. The extensive computational capacity of a single principal cell is seldom utilized at once. Dividing its full computational power into numerous subroutines that could be flexibly used according to momentary needs would be an enormous advantage. This important service is provided with ease by the interneuron system. Interneurons can functionally "eliminate" a dendritic segment or a whole dendrite, selectively inactivate Ca^{2+} channels, and segregate dendrites from the soma or the soma from the axon. In effect, such actions of interneurons are functionally equivalent to replacing a principal cell with a morphologically different type, thus functionally increasing component diversity of the principal-cell population

9. Mainen and Sejnowski (1996). Morphological features, and likely the associated differences of channel distributions, may be responsible for the differences between neuronal subtypes within the same layers, e.g., layer 5 bursting and nonbursting pyramidal neurons (Connors and Regehr, 1996).

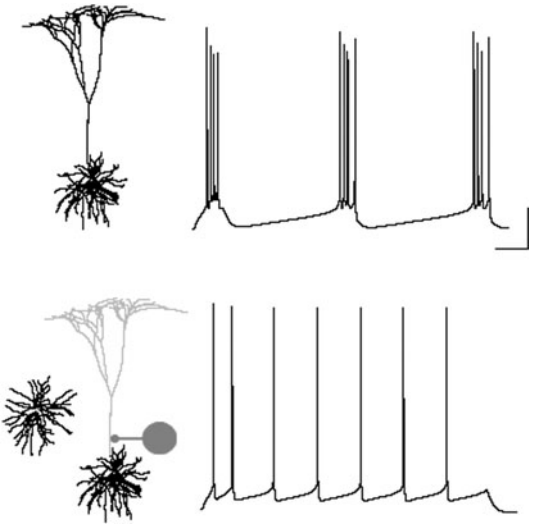

Figure 3.5. Inhibition can alter the firing patterns of neurons. Top: Burst firing pattern of a layer 5 model neuron. Bottom: Removal of the apical dendritic tree in the model neuron converts the burst discharge into a regular firing pattern. A similar effect in firing pattern can occur when the apical dendritic tree is isolated from the rest of the neuron by proximal dendritic inhibition. Model firing patterns are modified, with permission, from Mainen and Sejnowski (1996).

(figure 3.5). And the large family of interneuron species perform all these tricks in a matter of milliseconds.

Diversity of Cortical Interneurons

Brain systems with "simple" computational demands evolved only a few neuron types. For example, the thalamus, basal ganglia, and the cerebellum possess a low degree of variability in their neuron types. In contrast, cortical structures have evolved not only five principal-cell types but also numerous classes of GABAergic inhibitory interneurons. Every surface domain of cortical principal cells is under the specific control of a unique interneuron class. This is a clever way of enormously multiplying the functional repertoire of principal cells using mostly local interneuron wiring. Adding more interneurons of the same type linearly increases the network's combinatorial properties. However, adding novel interneuron types to the old network, even in small numbers, offers a nonlinear expansion of qualitatively different possibilities.[10]

10. Alvarez de Lorenzana and Ward (1987) distinguish between combinatorial expansion (linear) and generative condensation (nonlinear) for describing general properties of evolving systems.

Our view on cortical interneurons has changed dramatically during the past decade. What used to be thought of as a homogeneous collection of neurons providing negative feedback to the principal cells turned out to represent a large family of intrinsically different cells with unexpectedly complex circuit wiring. To date, there is not even a widely accepted taxonomy of interneurons, and novel types are being discovered literally monthly. Splitters and lumpers like to divide interneurons into, respectively, infinite or small numbers of categories. Péter Somogyi at Oxford University, Tamás Freund at the Hungarian Academy of Sciences, Budapest, and I suggested that the axonal targets of interneurons on the principal cells should be the first main division of interneuron classification.[11] The functional justification of this classification is that the main goal of the interneuron system is to enhance and optimize the computational abilities of the principal cells.[12] In their relation to the principal cells, three major interneuron families are recognized (figure 3.6).[13] The first and largest family of interneurons controls the output of principal cells by providing perisomatic inhibition. Output control is achieved at either the soma by basket cells or the axon initial segment by chandelier cells.[14] Interneurons of the second family target specific dendritic domains of principal cells. Every known excitatory pathway in the cortex has a matching family of interneurons. Several additional subclasses seek out two or more overlapping or nonoverlapping dendritic regions, and yet other subclasses innervate the somata and nearby dendrites with similar probability. Because the different domains of principal cells have different functional dynamics, interneurons innervating those specific domains adapted their kinetic properties to match

11. Interneuron classification advanced first in the hippocampus. See Halasy and Somogyi (1993), Buhl et al. (1994), Gulyás et al. (1993a), Sík et al. (1994, 1995), and Freund and Buzsáki (1996). For more recent progress, see the Interneuron Diversity series in *Trends in Neuroscience* (Mott and Dingledine, 2003; Freund, 2003; Maccaferri and Lacaille, 2003; Lawrence and McBain, 2003; Whittington and Traub, 2003; Jonas et al., 2004; Baraban and Tallent, 2004; Buzsáki et al., 2004; Monyer and Markram, 2004; Cossart et al., 2005). The most comprehensive treatment of interneuron diversity is the excellent book *Diversity in the Neuronal Machine* (Soltesz, 2006).

12. To date, the various classes, their connectivity, and functions are best characterized in the hippocampus, a cortical structure with a single principal-cell layer, because the full extent of the dendritic and axon arbors of *in vivo* labeled hippocampal interneurons has been quantified, and their physiological features have been extensively characterized in both slice preparations and behaving animals (Freund and Buzsáki, 1996; Klausberger et al., 2003, 2004). The wiring and functional principles derived from hippocampal interneurons appear to be identical or very similar in the isocortex (Somogyi et al., 1998; Markram et al., 2004; Somogyi and Klausberger, 2005).

13. This classification is based on the concept that the "goal" of inhibition is to provide the required spatiotemporal autonomy (segregation) for groups of pyramidal cells to execute a given function.

14. This beautiful name was coined by János Szentágothai (1975; Szentágothai and Arbib, 1974). He believed that the chandelier-like distribution of this neuron's boutons corresponded to dendritic synapses. It was Somogyi who, using his innovative combination of Golgi sections and electron microscopy, recognized that all boutons terminate on the axon initial segment of pyramidal cells (Somogyi et al., 1983). He introduced a new term, axoaxonic cell, but the more poetic chandelier cell is still widely used. A recent, unexpected finding is that chandelier cells may, in fact, *depolarize* the axon initial segment and thereby synchronize their target cells (Szabadics et al., 2006).

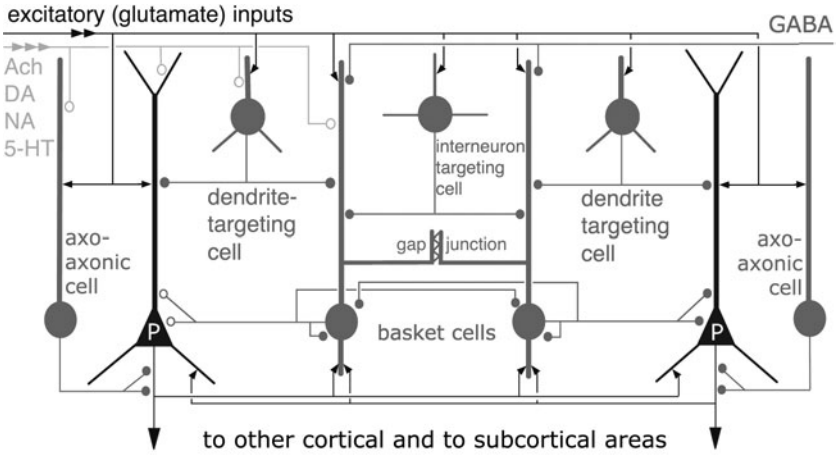

Figure 3.6. The basic cortical circuit, including one type of pyramidal cell (P) and representative interneuron classes. Perisomatic control of pyramidal cell is secured by basket and axoaxonic (chandelier) neurons. Both pyramidal cells and interneurons are innervated by extracircuit excitatory and inhibitory inputs as well as by subcortical neurotransmitters: acetylcholine (ACh), dopamine (DA), norepinephrine (NA), and serotonin (5-HT, 5-hydroxytryptamine). Modified, with permission, from Somogyi et al. (1998).

their targets. Not surprisingly, members of the dendrite-targeting interneuron family display the largest variability.

In addition to affecting the activity of principal cells, interneurons also innervate each other by an elaborate scheme and affect each other's biophysical properties. An important subgroup with at least some overlap with the dendrite-targeting family represents a special set of interneurons whose axon trees span two or more anatomical regions, and some axon collaterals cross the hemispheric midline and/or innervate subcortical structures, hence the term "long-range" interneuron.[15] Their distant clouds of terminal boutons are separated by myelinated axon collaterals that provide fast conduction speed for temporal synchrony of all terminals (figure 3.7). Such widely projecting, long-range neurons are rare, but in light of the functional importance of small-world

15. Before the landmark paper of Watts and Strogatz (1998) appeared, we reported on the "most peculiar anatomical features," as a reviewer of the manuscript put it, of a newly discovered interneuron type in the hippocampus (Sík et al., 1994). The flow of information in the hippocampus is mostly unidirectional, or so-called feedforward. The axons of our new neuron, in contrast, went in all directions, contacting neurons in all subregions of the hippocampus. We suggested that a few long-range neurons are sufficient to synchronize large territories of local networks. Long-range neurons have also been described in layers 2 and 6 of the neocortex. Their extensive axon trees cross cortical regions and connect similar regions of the two hemispheres (Peters et al., 1990; McDonald and Burkhalter, 1993). Similar to hippocampal long-range interneurons, most of them contain somatostatin immunoreactivity, neuropeptide Y, and/or neuronal nitric oxide synthase (Tomioka et al., 2005). Axon collaterals of some of the Martinotti cells (Martinotti, 1889) in the neocortex have been observed to enter the white matter.

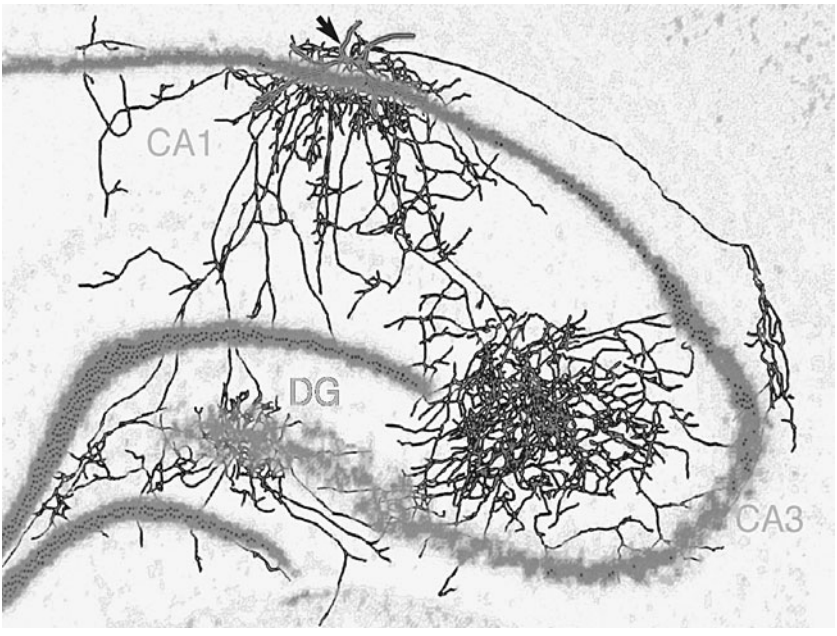

Figure 3.7. Axon collaterals of GABAergic interneurons can span different anatomical regions. The interneuron shown here projects back from the hippocampal cornu ammonis 1 (CA1) region to the dentate gyrus (DG) and the CA3 regions. Similar long-range interneurons project to subcortical sites, the contralateral hippocampus, or the entorhinal cortex. Reprinted, with permission, from Sík et al. (1994).

graphs, their role must be absolutely critical. They provide the necessary conduit for synchronizing distantly operating oscillators and allow for coherent timing of a large number of neurons that are not connected directly with each other.

The third distinct family of interneurons, discovered by Freund's group, has the distinguishing characteristics that their axons avoid principal cells and contact exclusively other interneurons.[16] The existence of these interneuron-specific interneurons provides mounting support for a unique organization of the inhibitory system. No principal cells are known that contact only other principal cells and avoid inhibitory interneurons. The interneuron-specific family also overlaps with the long-range subclass, again emphasizing the importance of interregional synchronization of inhibition, and consequent coherent oscillatory entrainment of their target principal-cell populations.[17]

The cell bodies and dendrites of interneuron families in the first divisions of our taxonomy can be found in different layers, and their differential inputs can

16. Gulyás et al. (1996) and Freund and Gulyás (1997).

17. This taxonomy is based mostly on interneuron classes of the hippocampus, but it also holds in the neocortex (Somogyi et al., 1998; Markram et al., 2004).

compose the basis of the second division. With perhaps 20 or more distinguished interneuron types in the rodent cortex, the complexity of their wiring must be enormous, although the critical details are not yet known.[18] Furthermore, interneurons within the same family can communicate with each other via electrical synapses. These are pores between adjacent membranes of two neurons, called gap junctions, that allow bidirectional flow of ions and small molecules.[19] In addition to releasing GABA, interneurons also manufacture various calcium-binding proteins, such as parvalbumin, calbindin, and calretinin, as well as a variety of different peptides. Many of these peptides, such as cholecystokinin, somatostatin, and vasointestinal peptide, are hormones and polypeptides with known endocrine and blood-flow–regulating roles in the body. They thus not only are convenient markers for anatomists but also could play hitherto poorly understood roles in communicating the state of interneurons to the principal cells, glial cells, and brain vessels.[20]

The advantage of varying the surface domain innervation of the principal cells by the different interneuron classes becomes especially clear when temporal dynamics are also included. The biophysical properties of interneurons vary substantially across the groups, and as a result, they can be recruited differentially at different firing frequencies of the principal cells. For example, basket cells respond with decreasing efficacy when stimulated by high-frequency inputs because of their "depressing" input synapses, which function as a low-pass frequency filter. In contrast, several types of dendrite-targeting interneurons fail to generate spike output when driven at low frequency and require several pulses before they begin to discharge because their input synapses are of the facilitatory type. These interneurons therefore can be conceived as a high-pass frequency filter. The consequence of such dynamics is easy to visualize.[21] When a pyramidal neuron discharges at a low rate, it activates almost exclusively its perisomatic interneurons. On the other hand, at a higher discharge rate, the somatic inhibition decreases, and inhibition is shifted to the dendritic domain (figure 3.8). Time is thus transformed into subcellular space, due to the frequency-filtering behavior of synapses.

The Interneuron System as a Distributed Clock

Despite its multifarious wiring, the principal-cell system alone cannot carry out any useful computation. It is the inhibitory neuronal network, when coupled to

18. For a recent review, see Somogyi and Klausberger (2005).

19. Gap junctions tend to occur within the same types of interneurons (Katsumaru et al., 1988; Connors and Long, 2004; Hestrin and Galarreta, 2005).

20. Given the high diversity of interneuron types, it is unlikely that all types innervate each and every pyramidal cell in the cortex (Markram et al., 2004). Thus, in addition to diversify the functions of single cells, interneurons can diversify microcircuits, as well, by introducing inhomogeneities at dynamically changing time scales.

21. Thomson (2000a,b), Gupta et al. (2000), and Pouille and Scanziani (2004).

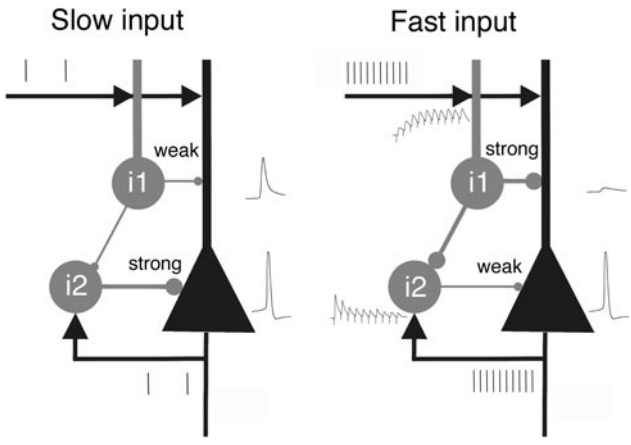

Figure 3.8. Input frequency determines spatial dominance of inhibition. Left: At a slow input frequency, feedforward dendritic inhibition is weak. Action potentials in the pyramidal cell body back-propagate into the dendrite. Right: At fast input frequency, the dendrite-targeting neuron (i1) is potentiated, whereas the drive of the soma-targeting interneuron (i2) is depressed. The result is decreased inhibition of the soma and increased inhibition of the dendrite. Back-propagation of the action potential to the pyramidal cell dendrite is attenuated by the enhanced dendritic inhibition. Pouille and Scanziani (2004) have demonstrated that fast input activation shifts inhibition from the soma to the dendrites. Dendritic inhibition, in turn, suppressed somadendritic propagation of the action potential and dendritic Ca^{2+} influx (Tsubokawa and Ross, 1996; Buzsáki et al., 1996).

the principal cells, that provides the flexibility needed for the complex operations of the brain. An important goal of single neurons and neuronal networks is to respond efficiently but selectively to incoming inputs. In a single cell, the former goal can be achieved by keeping the so-called "resting membrane potential" of principal cells just below spike threshold. This task is difficult to achieve due to the nature of thresholds. The threshold concept is identical to that of the phase transition between ice and water. In both cases, a minimal external force is needed to bring about a state change. A difficult problem, implicit in the concept of threshold, is the neuron's sensitivity to noise. If the membrane potential was just below threshold all the time, any minor increase in excitation would discharge the cell. Furthermore, this would be energetically a very expensive mechanism because complicated machinery would be required to "clamp" the membrane to a narrow voltage range against a background of fluctuating temperature, pH, and other factors in the brain environment. If the membrane is protected from noise by a more negative resting membrane potential, the production of an action potential output would require stronger depolarization, which is also energetically costly. An alternative solution is to move membrane potential up and down in a coordinated manner across neurons. The only disadvantage of this solution is that the same external input applied repeatedly will have different consequences in

each case, depending on the centrally coordinated mechanism of threshold adjustment. There will be short windows of opportunity when the membrane potential is elevated to just below threshold, alternating with times when the input remains subthreshold because of the transient hyperpolarized state of the neurons. This inconvenience, however, is amply balanced by the lower energy cost. Fluctuating the membrane potential is energetically much less costly than keeping it at a constant depolarized level.[22] The important job of swinging the membrane potential of principal cells is subcontracted to the interneuron system, and the mechanism is oscillation.

Balance of opposing forces, such as excitation and inhibition, often gives rise to rhythmic behavior. Oscillators consisting of only excitatory pyramidal cells also exist, as is the case when GABAergic receptors are blocked pharmacologically. In such cases, the frequency of hypersynchonous, epileptic oscillations is determined primarily by the intrinsic biophysical properties of the participating pyramidal cells and the time course of neurotransmitter replenishment after depletion. Under physiological conditions, oscillations critically depend on inhibitory interneurons. In fact, providing rhythm-based timing to the principal cells at multiple time scales is one of the most important roles of interneurons.

Let us first consider the simplest possible oscillating network that consists of similar types of interneurons, for example, synaptically connected basket cells. Interneuronal networks without an external excitation would not do much, of course, except remain silent. A transient excitation would generate only a transient oscillatory response, which would die away quickly. In order to maintain an oscillation, some external force is needed to generate spiking activity. Since the only requirement of such an external force is to maintain some firing, this role can be played by a subcortical neurotransmitter or ambient glutamate excitation, each of which can maintain a sufficient level of tonic depolarization. Activity of interneurons, in turn, can give rise to some order. The simplest case is when all or some interneurons themselves display an oscillatory response, and inhibitory coupling can link them into an oscillating network.[23]

However, even if none of the interneurons oscillates in isolation, the synaptically connected homogeneous interneuron network can still give rise to sustained oscillations. The intuitive interpretation of collective rhythm in interneuron

22. Such temporal sampling solutions are also used at the behavioral level. To get odor samples in proper doses, vertebrates rhythmically sniff and arthropods flick their olfactory appendages with characteristic frequency and duration after detecting an odor. Such active fluctuation of the input greatly enhances odor detection (Laurent, 1999).

23. The external force, of course, is vital. Networks consisting of inhibitory neurons only cannot sustain any activity. Sustained activity requires regenerative positive feedback, typically supplied by recurrent excitation. Networks without recurrent excitatory loops (e.g., the cerebellum) do not possess spontaneous or self-organized network activity (see Cycle 13).

networks is the following. In the initial state, interneurons discharge randomly. Due to chance, some of them may discharge together in a short time window. This group of neurons will impose stronger inhibition on their targets than other randomly discharging neurons. As a result of this stronger inhibitory seed, more neurons will be silenced simultaneously, after which their probability of discharging together upon recovery increases.[24] Now, we have a larger group of synchronously discharging cells which, in turn, will silence an even larger portion of the population, increasing their probability to fire together once inhibition fades away. With appropriate connectivity and conduction delays, eventually most or all neurons in the inhibitory network will be inhibited at the same time and fire synchronously after inhibition wears off. Discharge and silence will alternate in all parts of the network synchronously. Not all interneurons need to discharge at every cycle, and the oscillation can be maintained as long as a sufficient portion of interneurons fire at each cycle. The mean time difference between the discharges of any two pairs of cells is zero; that is, interneurons discharge synchronously at approximately the same time, independent whether the cell pairs are connected bidirectionally, one way only, or not at all, as long as they are part of the same network. The frequency of the oscillation depends only on the average duration of inhibition, which is the critical time constant in the distributed interneuron clockwork. If inhibition is mediated by fast-acting $GABA_A$ receptors, the oscillation frequency will correspond to the gamma frequency band (40–100 hertz). Changing the time constant of the $GABA_A$-receptor–mediated GABA response will affect the beat frequency of the interneuron network oscillator.[25]

Because interneurons connected by $GABA_A$ receptors are ubiquitous throughout the brain, it is not surprising that gamma-frequency oscillation can arise in almost every structure. In such "gamma clocks," no single neuron is responsible for initiating or maintaining the oscillation, yet all of them contribute to the rhythm whenever they fire. The responsibilities are distributed, and the result depends on cooperation. Once a collective pattern arises, it constrains the timing of the action potentials of the individual cells because of the collectively generated inhibition (figure 3.9). Thus, there are multiple causes/requirements at various levels. Firing

24. Because $GABA_A$-receptor–mediated inhibition is mediated by Cl^-, whose equilibrium potential is close the resting membrane potential, inhibition is not necessarily hyperpolarizing but "shunting" (i.e., increased membrane conductance). For a contribution of shunting inhibition in oscillations, see Vida et al. (2006).

25. Inhibition-based oscillators have been known for a long time in simple networks, consisting of a few neurons only. In such circuits, neurons reciprocally suppress each other's activity and therefore spike out of phase (Marder and Calabrese, 1996). In-phase synchrony, brought about by inhibition, has been demonstrated both in brain slices maintained *in vitro* and in computer models. For computational models leading to the above ideas, see Wang and Rinzel (1993), Lytton and Sejnowski (1991), Ermentrout and Kopell (1998), White et al. (1998a and b), Whittington et al. (1995), Traub et al. (1996, 1999), and Wang and Buzsáki (1996). Inhibitory neurons, in turn, can effectively synchronize target principal cells (Lytton and Sejnowski, 1991; Buzsáki and Chrobak, 1995; Cobb et al., 1995).

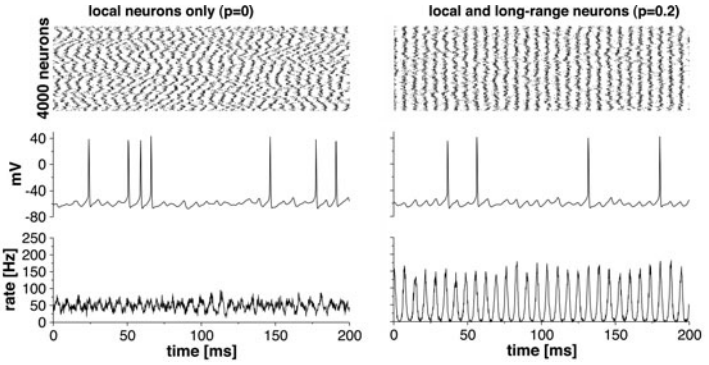

Figure 3.9. In networks with only local inhibitory connections, no oscillations emerge (left: top, spike raster of individual neurons; middle, voltage trace of a single representative cell; bottom, population synchrony). Adding a small subset of long-range interneurons to the locally connected population, with 20 percent of the contacts distributed according to a power-law distribution, robust oscillation emerges (right). Reprinted, with permission, from Buzsáki et al. (2004).

and connectivity are essential, but the exact wiring is not critical as long as enough convergence and divergence are present. On the other hand, the oscillation as a group-level behavior decreases the timing freedom of all neurons. Once the network is engaged in an oscillation, the convergent inhibition from multiple partners confines the windows of opportunity for the neurons to discharge. This top-down constraint is as important as the bottom-up contribution of the individual members. Therefore, oscillation in the GABAergic interneuron network is a truly emergent event, governed by both elementary (i.e., bottom-up) and statistical (top-down) causes.

Let us now add pyramidal neurons to the interneuron network. Intuitively, what we expect to see is the following. Because of the synchronous discharge of interneurons, now both interneurons and pyramidal cells are inhibited rhythmically and at the same time. So if the pyramidal cells are also activated by some random external force, they discharge with the lowest probability when all neurons are inhibited and with a higher probability at times when least inhibited, that is, at the same time as the interneurons. Thus, on average, all neurons will fire at a zero time lag and will be silenced at the same time. This scenario is best observed during epileptic discharges and autonomous conditions when outside influences exert very little effects on the internal pacing of the population. However, under physiological conditions, oscillator networks made from homogeneous inhibitory neurons are easy to disrupt because small perturbations in timing can have a large deteriorating effect on subsequent synchronous discharge of the neurons. This may explain why gamma-frequency oscillations are typically short-lasting, transient events. Introducing some heterogeneities, for

example, strong pyramidal cell–interneuron coupling, can interfere with the rules because now locally active pyramidal cells can also affect timing of the interneurons.[26]

How can a "distributed clock" of neurons with finite axon conduction and synaptic delays grow in larger brains? Simultaneous inhibition of all neurons is possible only if inhibition arrives to all neurons more or less at the same time. Inserting just 1 millisecond of delay between each pair of neurons in a chain or a two-dimensional lattice of neurons may prevent the coherence of the activity at high frequencies. Some mechanisms are needed to compensate for the ever-growing delays. The various solutions that are used to compensate for the delays in different parts of the brain are discussed in subsequent Cycles. For now, let us consider how the wiring relationship among the various classes of interneurons can be maintained in growing brains.

Scaling Interneuron Connections in Growing Brains

The primary role of the interneuron networks is to coordinate timing of the action potentials. This task becomes more and more complex as the brain grows because neurons are placed farther apart from each other. Owing to the limited axon conduction velocities, the growth in volume should somehow be compensated for if the goal is to keep the timing of principal cells constant even if those cells reside in distant cortical modules. How this is done is not exactly clear. Below, I consider a few possibilities.

If we know little about the types of interneurons, we know even less about the relative frequency of cells in each interneuron class. As discussed above, the numbers of neurons in each primary and secondary division vary considerably. The most numerous interneuron types belong to the perisomatic control group, followed by the dendrite-controlling groups, which innervate single or multiple dendritic domains; the least numerous cells belong to the long-range interneuron family. Independent of whether we subscribe to the "repeating module" concept of the cortex or emphasize its small-world-like connectivity features, the relative incidence of interneurons in the major divisions and the numerous subdivisions are expected to have some mathematically definable relationship. It is highly unlikely that proportions of interneurons in the different divisions (classes) with different extents of axonal projections would scale proportionally in growing brains for the same reasons discussed for the principal cells (Cycle 2). If a defined connectivity is necessary for oscillatory timing of principal cells in a small rodent brain, then how should the network be wired in the human brain so that the same timing function is preserved?

26. I discuss oscillators based on pyramidal cell–interneuron interactions in Cycle 9.

The textbook recommendation for interneuron wiring is local connections, including critical gap junctions among dendritically overlapping interneuron populations. However, this creates a different but related problem: physically distant neurons are not connected to each other, and this "disconnectedness" increases monotonically with network size. Synaptic path length and, consequently, synaptic and conduction delays become excessively long for synchronization in larger networks. We need a mechanism that can compensate for the delay. The solution for interneuron networks is the same as for principal cells: shortcuts. Such shortcuts are accomplished by the long-range interneurons, which connect local interneurons residing in different cortical regions. Now we can expect from the small-world rules discussed in Cycle 2 that the fraction of long-range interneurons in large brains will decrease substantially.[27]

The general conclusion that we can draw from the above discussion is that the same physiological function in different-sized brains is supported by circuits with different compositions of neuronal proportions and connectivity, which have to be explored in the brains of each species to identify the particular wiring schemes. Nevertheless, these quantitatively different architectures should have some mathematically predictable relationships. This reasoning, of course, assumes that all mammalian brains are built from essentially the same interneuron types with similar connectivity principles. An alternative or complementary solution would be to increase the diversity of interneuron types with the evolution of the mammalian cortex. To date, there are no data available for such hypothetical enrichment.[28]

In the last century, we went as far as we could to uncover and describe the microscopic and macroscopic components of the brain. Progress over the past decade brought us closer than ever to understanding the true nature of brain topology. Now, it is time to see the functional consequences of this intricate wiring. To achieve that, in the remaining Cycles I focus on the dynamics that take place in the brain web.

Briefly . . .

In addition to principal cells, the cerebral cortex contains diverse classes of interneurons that selectively and discriminately innervate various parts of principal cells and each other. The hypothesized "goal" of the daunting connectionist schemes of interneurons is to provide maximum functional complexity. Without inhibition and dedicated interneurons, excitatory circuits cannot accomplish anything useful. Interneurons provide autonomy and independence to neighboring

27. Changizi (2003) is an excellent source of the various scaling laws in the brain. It describes physicomathematical models for numerous allometric (i.e., differential growth) relationships.

28. According to Lorente de Nó (1949), the morphology of cortical neurons becomes less uniform and the number of nonpyramidal neurons increases as one ascends the phylogenetic scale. Yet, very few comparative data are available to support or dispute this challenging claim.

principal cells but at the same time also offer useful temporal coordination. The functional diversity of principal cells is enhanced by the domain-specific actions of GABAergic interneurons, which can dynamically alter the qualities of the principal cells. The balance between excitation and inhibition is often accomplished by oscillations. Connections among interneurons, including electrical gap junctions, are especially suitable for maintaining clocking actions. Thus, the cerebral cortex is not only a complex system with complicated interactions among identical constituents but also has developed a diverse system of components.

Cycle 4

Windows on the Brain

> We shall not fail or falter; we shall not weaken or tire. . . . Give us the tools and we will finish the job.
>
> —Winston Churchill

The quote from Churchill sounds like an honest promise, but one might suspect that it is just empty political rhetoric. Of course, if someone gives us the right tools, we can succeed in anything. The usual problem is, however, that first one has to invent those tools to succeed. To monitor the ever-changing patterns of brain activity, neuroscientists need methods with sufficient spatial and temporal resolution. The definition of "sufficient" in this context is a complex issue because it varies with the level of analysis and expectation.

There are only a handful of tools at the neuroscientist's disposal to monitor brain activity without seriously interfering with it. Can we finish the job with these tools alone? Maybe not, but for now, we have to live with them and believe that we will not fail or falter. Each of the existing methods is a compromise between spatial and temporal resolution. The desired temporal resolution is the operation speed of neurons, that is, the millisecond scale. The desired spatial resolution depends on the goal of the investigation and expands from the global scale of the brain down to the spines of individual neurons. No current method is capable of continuously zooming from the decimeter to the micrometer scale, which is why several methods are being used, often in combination. Finding the optimal level of resolution always depends on the question asked. This Cycle summarizes the methods used for the exploration of brain activity, emphasizing mostly those techniques that are most frequently used for monitoring oscillatory

behavior of neuronal networks. If you have taken an introductory level class in neurophysiological methods, feel free to skip it and come back if you need further clarification.

EEG and Local Field Potential Recording Methods

Hans Berger's noninvasive recording technique is still the most widespread method used in clinical and psychological laboratories. The galvanometers are now in museums; the voltage changes are now detected by highly sensitive amplifiers and the traces are stored on fast computers. Recording EEG traces from a few sites is sufficient to determine whether the brain is alive or dead or whether it is sleeping or awake. However, deciphering the precise spatiotemporal changes in the brain and how they are associated with the experience of, say, enjoying a Jackson Pollock canvas or of remembering your first date is an entirely different challenge. Increasing the number of recording sites is very useful only up to a limit, because scalp electrodes placed too close together will sense pretty much the same electrical fields without further enhancing spatial resolution (figure 4.1). (Please note that the term "field" is often used differently by neurophysiologists and physicists. For a neurophysiologist, the field or local field means extracellular potential or EEG. For a physicist, field refers to a force defined at every point of space generated by electric charge. The gradient of the field is the extracellular potential.) In contrast to the excellent temporal resolution, scalp recording EEG methods have serious spatial resolution problems that cannot be easily overcome, for the reasons explained below.

With several recording sites on the scalp, a map of the brain's electrical changes can be constructed. The mapping technique was not invented by neuroscientists or neurologists. Seismologists have used an identical method in their effort to predict the time and place of destructive earthquakes. Our planet is covered by thousands of seismograph stations. These stations transmit their data for centralized real-time processing. The online processed data are disseminated to concerned national and international agencies, which maintain an extensive, global seismic database on earthquake parameters. Despite the eight-digit dollars spent annually, the spatiotemporal resolution of earthquake predictions, as we know, is far from adequate. The seismologists' task is literally identical to that of a neurologist who attempts to localize the source of an epileptic seizure from scalp recordings. The source localization problem or, as engineers call it, the "inverse problem" is the task of recovering the elements and location of the neural field generators based on the spatially averaged activity detected by the scalp electrodes. However, surface recordings provide only limited information about the structures and neuron groups from which the hypersynchronous epileptic activity emanates, and the inverse problem does not have a unique solution. Localization of physiological, less synchronous patterns that generate

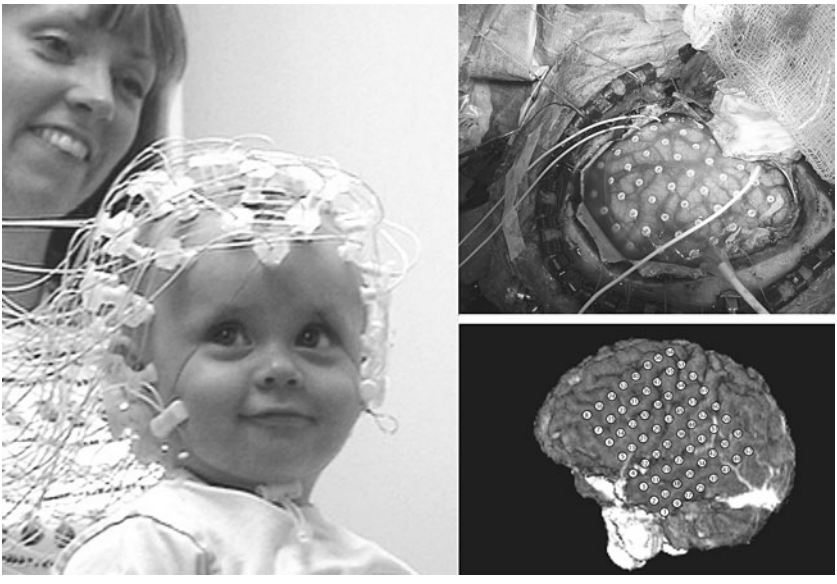

Figure 4.1. Electrical activity of the cerebral cortex can be monitored by multiple electrodes placed on the scalp ("geodesic" helmet, left). Better spatial resolution can be achieved by subdural "grid" electrodes: intraoperative placement of the subdural grid after craniotomy (top right) and the estimated electrode positions of the recording sites based on the patient's structural MRI (magnetic resonance imaging) scan acquired after the electrodes were implanted (bottom right). Infant photo is courtesy of A. Benasich, Infancy Studies Laboratory, Rutgers University; photo of grid electrodes is courtesy of R.T. Knight and R. Canolty, University of California–Berkeley.

much smaller amplitude extracellular currents and fields is even more difficult. Furthermore, numerous brain source configurations can produce identical electromagnetic fields on the scalp, especially when measured at only a finite number of electrode positions. The difficulty of source localization has to do with the low resistivity of neuronal tissue to electrical current flow, the capacitive currents produced by the lipid cell membranes, and the distorting and attenuating effects of glia, blood vessels, pia, dura, skull, scalp muscles, and skin. As a result, the EEG, recorded by a single electrode, is a spatially smoothed version of the local field potentials under a scalp surface on the order of 10 cm^2 and, under most conditions, has little discernible relationship with the specific patterns of activity of the neurons that generate it.[1] The spatiotemporal integration problem of neuronal activity is similar to statistical mechanics of physics in the sense that the specific details of the neuronal interactions are replaced by the typical average behavior. The EEG recorded from the scalp samples mostly the synaptic activity that

1. Nuñez (1998; 2000).

occurs in the superficial layers of the cortex. The contribution of deeper layers is scaled down substantially, whereas the contribution of neuronal activity from below the cortex is, in most cases, virtually negligible. This "fish-eye lens" scaling feature of the scalp EEG is the major theoretical limitation for improving its spatial resolution.[2]

Depth Electrode and Subdural Grid Recordings

Precise localization of the anatomical structures that give rise to the physiological abnormality is imperative in some clinical situations when the tissue has to be removed surgically. In these difficult cases, several wire electrodes are implanted into the suspected region, through which the locally generated extracellular field potentials can be monitored, a method routinely used in animal experiments, as well.[3] A less invasive approach that yields localization effectiveness somewhere between scalp recording and electrodes placed inside the brain is the subdural grid electrode (figure 4.1). The grid, a flexible strip with 20–64 rectangularly arranged electrodes, is introduced subdurally. Although inserting the grid by removing a bone flap in the skull and placing it directly on the cortical (pial) surface still requires surgery, both its implantation and removal are less invasive and less risky than those of deep wire electrodes. The amplitude of the electrocorticogram recorded by the grid electrodes is an order of magnitude larger than that of the scalp EEG. The signals provide better spatial localization because the electrodes integrate activity from a smaller brain area and are essentially free of muscle, eye-movement, and other artifacts ubiquitously present in the scalp EEG of waking, moving patients. Although these are superior features, the invasive grid electrode recording technique cannot be used for research in healthy humans because of ethical considerations. Fortunately, there is another method that can noninvasively increase spatial resolution, while keeping the advantage of the outstanding temporal resolution of the EEG. This technique monitors the magnetic rather than the electric fields of the brain.

2. Current density on the scalp (a measure of the volume conduction of current through the skull and into the scalp, generated by the neurons) is sensitive mainly to superficial sources, with sensitivity falling off at approximately r^4 (r = distance from a current source or sink to the scalp surface; Pernier et al., 1988) and insensitive to deep current sources in the brain. Scalp current density is the spatial derivative of current flowing into and through the scalp.

3. Local field potentials are usually recorded by small-sized electrodes, e.g., a wire tip placed in the depth of the brain, and reflect transmembrane activity of neurons in a more confined space than does the scalp electroencephalogram (EEG). By definition, local field potential and EEG are synonymous terms, but for historical reasons, EEG usually refers to scalp-recording field potentials. Activity recorded by electrodes placed directly on the brain surface is called an electrocorticogram (ECoG). Deep electrodes are most often used in patients with intractable epilepsies (Spencer, 1981; Engel, 2002).

Magnetoencephalography

Luckily, Berger was a physician, not a physicist. Had he understood Maxwell's equations, he would not have started recording electricity from his son's scalp in his search for the carrier mechanisms of telepathy.[4] Electricity needs a conductor to propagate, and air is a poor conductor; thus brain currents do not go beyond the scalp. However, voltage changes are accompanied by magnetic field changes. Because the brain generates electromagnetic currents, they can be detected outside the skull. The technical challenge one has to face, however, is dealing with the very small magnitude of magnetic fields generated by neuronal activity. The magnetic fields that emanate from the brain are only one hundred millionth to one billionth of the strength of Earth's magnetic field (or < 0.5 picotesla)! The sensor that can detect such weak signals is known as a SQUID (superconducting quantum interference device), a truly cool machine: it operates at –270°C. In essence, it consists of a superconductive loop and two Josephson junctions.[5] Liquid helium in the SQUID chills the coils to superconducting temperatures. Like with EEG, we need many sensors around the head to increase spatial resolution. The detector coils are placed as close to each other as possible, forming a spherical honeycomb-like pattern concentric with the head (figure 4.2).

A practical advantage of magnetoencephalography (MEG) is that no electrodes need to be attached to the scalp because the magnetic field emerges from the brain through the skull and the scalp without any distortion. The subject's head is simply fixed close to the surrounding coils. In contrast to the EEG, the MEG signal reflects mostly intracellular currents. Partly for this reason, MEG and EEG "see" different types of activity. For example, the radial sources that form the best dipoles for scalp EEG are not well detected by MEG. Only currents that have a component tangential to the surface of a spherically symmetric conductor produce a magnetic field outside the scalp. This fact favors detection of activity mainly from the fissures of the cortex. The spatial resolution of MEG is better than that of the EEG (ideally less than a centimeter), mostly because, in contrast to the EEG, the magnetic fields are not scattered and distorted by inhomogeneities of the skull and scalp.[6] Nevertheless, in practice, MEG source localization is still not accurate because the model assumptions are overly simplified and

4. Maxwell's equations are a set of partial differential equations that describe and predict the behavior of electromagnetic waves in free space, in dielectrics, and at conductor–dielectric boundaries. Magnetic waves, generated by neurons, therefore can be sensed outside the brain and head. Unlike the electric potential field, which is a scalar quantity, the magnetic field is a vector.

5. Brian D. Josephson was a graduate student at Cambridge University when he calculated in 1962 that electrical current would flow between two superconducting materials, even when separated by a nonsuperconductor or insulator, known today as the Josephson junction. The discovery of the tunneling phenomenon, or the "Josephson effect," led to the design of SQUIDs. David Cohen (1968) detected the first magnetic waves of the brain (occipital alpha oscillation).

6. Hämäläinen et al. (1993) provide detailed theoretical background for the MEG and SQUIDs and compares EEG and MEG signal detection problems.

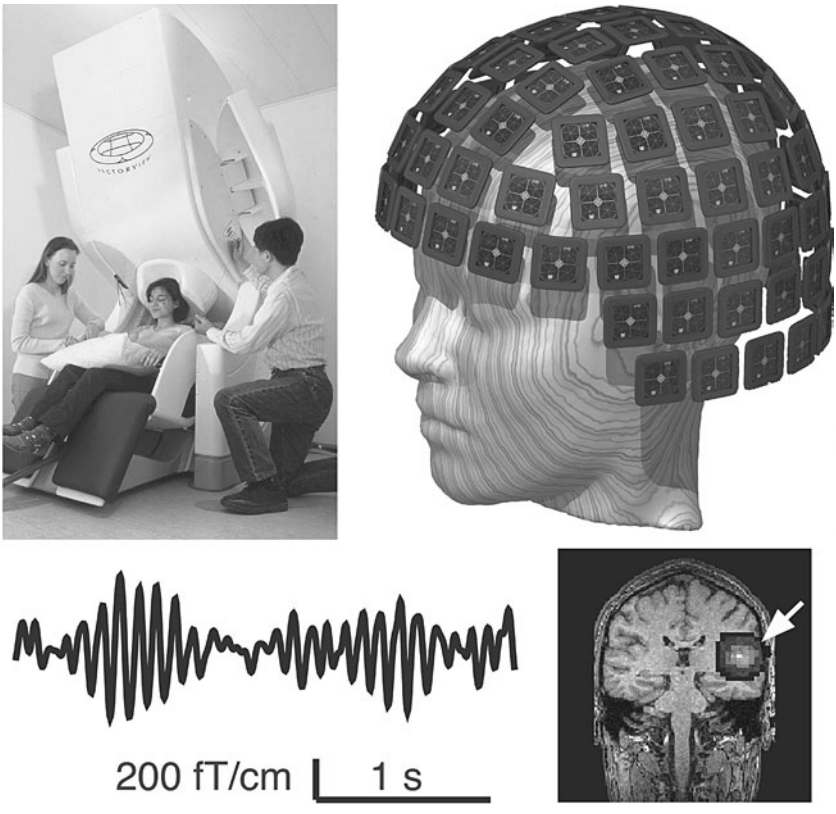

Figure 4.2. Magnetoencephalography (MEG) can detect brain responses outside the skull. The neuromagnetometer can record from numerous sites over the cerebral cortex (top panels). The example shown at the bottom is a spontaneous oscillation in the superior temporal lobe (lower right, arrow) at approximately 10 hertz (the auditory tau rhythm, part of the alpha family; see Cycle 7). Auditory stimulation suppresses the rhythm. The MEG source of the tau rhythm is described in Lehtela et al. (1997) and discussed in Cycle 7. Figure courtesy of R. Hari and M. Seppä, Brain Research Unit, Helsinki University of Technology.

are not adequate to represent the complexity of the physics and physiology involved in the human brain. Even under ideal conditions, the improved spatial resolution of MEG is insufficient to obtain information about local circuits and layer-differential effects in the cortex or about neuronal spikes, the necessary requirements for revealing not only the locations but also the mechanisms of neuronal operations.

Origin of Local Field Potentials

The signals measured by EEG and MEG reflect the cooperative actions of neurons. Not only neurons but also glia and even blood vessels can contribute to the

mean field measured by EEG and MEG, but in order to keep things simple, let us ignore the latter for the moment. The "mean field" measured outside the neurons in the extracellular space simply reflects the "average" behavior of large numbers of interacting neurons. The large degree of freedom—the essence of brain activity—is thus replaced by the "typical" average behavior. The exact nature of such cooperation is, of course, the million dollar question. Before attempting to address this complex question, let us begin with a single neuron.

Neurons Communicate with Spikes

Neurons share the same characteristics and have the same parts as other cells in the body, but they can pass messages to each other over long distances through their axonal processes. Like virtually any cell in the body, neurons have a high concentration of ions of potassium (K^+) and chloride (Cl^-) inside and keep the sodium (Na^+) and calcium (Ca^{2+}) ions outside. This arrangement produces a small battery that maintains a voltage difference of –60 millivolts relative to the world outside of the cell membrane. This ion separation is perhaps attributable to our single-cell ancestors and where they came from: the sea. Given the high concentration of Na^+ in seawater, keeping Na^+ outside the cell was a smart choice. However, when more developed organisms migrated to land, they had to carry the sea with them to maintain the same extracellular environment. For this purpose, the circulation of lymph and blood developed. All our cells are constantly bathed in water, more precisely, salt water. Each cell's membrane is perforated by myriads of small pores, appropriately called channels, through which ions can move in and out. Neurons can open and close these ion channels very quickly, thereby altering the flux of ions and, as a consequence, the voltage difference across the membrane. For example, the Na^+ channel opening initially occurs linearly with time, with a consequent linear decrease of the voltage difference between the inside and outside of the membrane: the neuron depolarizes. However, after some critical amount of Na^+ crosses the membrane, something entirely novel occurs. At this critical threshold, Na^+ influx will facilitate the opening of additional Na^+ channels, leading to an avalanche of Na^+ influx. This fast, strongly nonlinear event will depolarize the membrane so that the inside becomes positive by about 20 millivolts, as if the battery was reversed temporally. This fast depolarizing event is portrayed by the rising phase of the action potential (figure 4.3). At this voltage level, the process stops mostly due to another feature of the membrane, the voltage-dependent inactivation of Na^+ channels.

Pumping all the excess Na^+ out of the neuron is a lengthy process. To regain the resting voltage across the membrane more rapidly, neurons opted for another strategy: voltage dependence of K^+ channel activity. As the action potential reaches its peak, the voltage-dependent K^+ channels are activated and quickly repolarize the cell. This fast repolarization is the falling phase of the action potential (figure 4.3). Thus, the positive charge created by the influx of Na^+ is compensated for by the quick efflux of equal charges carried by K^+. This push-pull process, active during the action potential, takes about a millisecond (absolute refractoriness) and limits the maximum firing rate of the neuron. Because the action potential appeared as a

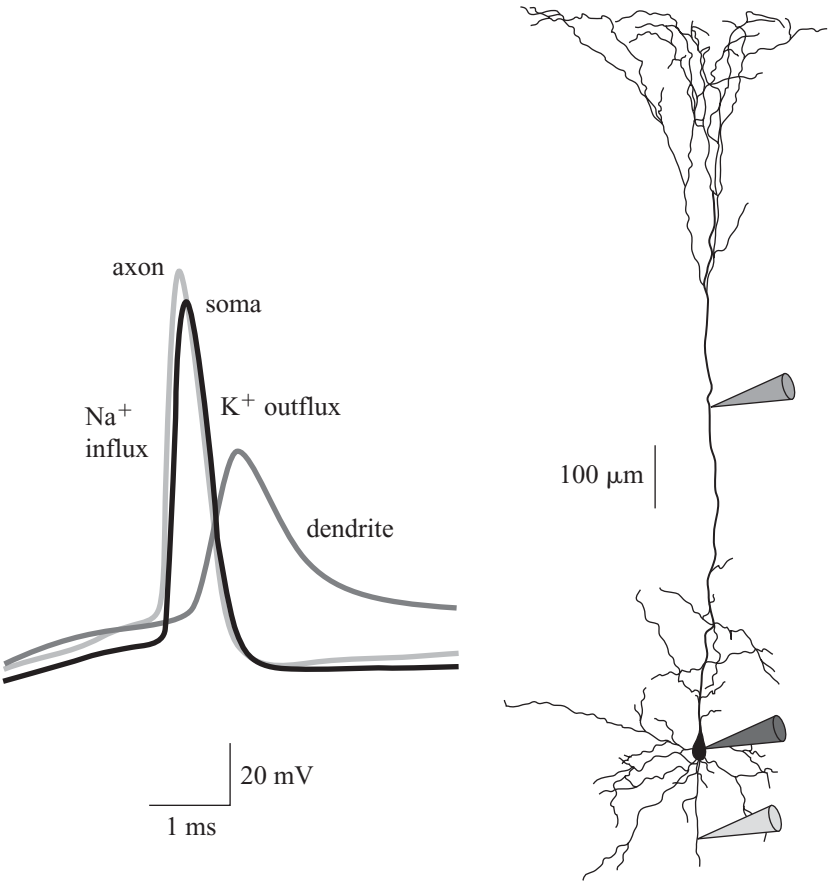

Figure 4.3. Fast action potentials propagate forward to the axon collaterals and backward to the dendrites: action potential waveforms (left) recorded with patch pipettes (described further below; see note 24) from the axon, soma, and dendrite in a layer 5 pyramidal neuron (right). Note delays and the different kinetics of Na^+ influx (rising phase of spike) and K^+ outflux (falling phase) and the associated different waveforms of the voltage traces. Reprinted, with permission, from Häusser et al. (2000).

short, large-amplitude event on the early chart recorders, investigators called the action potential a "spike." So when we refer to a spiking or firing neuron, what we really mean is that the neuron gives rise to action potentials.

In contrast to the megahertz speed of computers, the speed of spike transmission by neurons is limited to a maximum of a few hundred events per second. Nevertheless, once an action potential is initiated, it can propagate through the entire axon tree of the neuron and signal this event to all its downstream targets.[7]

7. Although failures may occasionally occur at junctions or in the terminals at higher frequencies, the current view is that the low-frequency action potential travels to all presynaptic boutons.

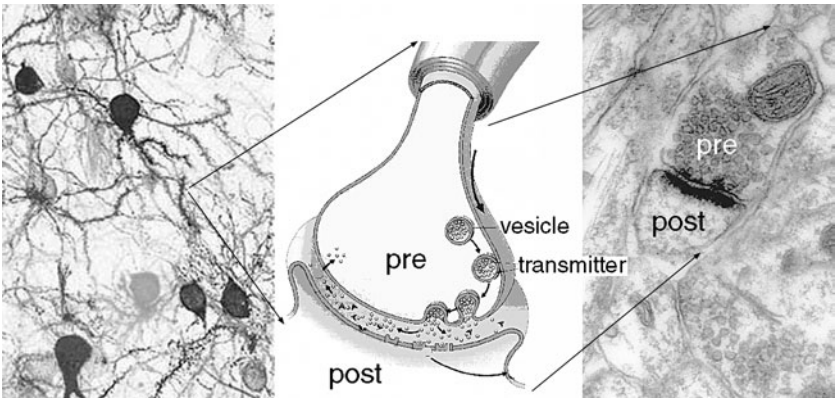

Figure 4.4. Neurons communicate mainly with chemical synapses. Left: Neural tissue with somata, dendrites, spines, and axons. Middle: An axon terminal (presynaptic, pre) in synaptic contact with a target (postsynaptic, post) neuron. Neurotransmitter is packaged into vesicles in the axon terminal. Upon arrival of an action potential and associated Ca^{2+} influx into the terminal, the vesicle empties its contents into the synaptic cleft, and the neurotransmitter binds onto its receptors in the postsynaptic membrane. Right: Electron microscopic picture of the synapse. Courtesy of T.F. Freund.

Again, compared to the traveling velocity of electricity in computer circuits, propagation of action potentials is quite sluggish at 0.5–50 meters per second, depending on the caliber and insulation type of the axon cable.[8] This slow transfer of neuronal information by the traveling action potentials is the most important limiting factor in the speed performance of neuronal networks.

Synaptic Potentials

Neurons are also good listeners, very much interested in what their upstream peers have to say. At the contact point of each axon terminal or "bouton," there is a thin physical gap between the membrane of the axon terminal and the membrane of the sensing neuron. This membrane–gap–membrane triad is called the synapse (figure 4.4). The presynaptic terminal is specialized to release a chemical substance, appropriately called a neurotransmitter, which then binds onto specialized receptors on the postsynaptic side. All cortical pyramidal cells release glutamate, which depolarizes and discharges the target neurons; therefore, glutamate is referred to as an excitatory neurotransmitter. In contrast, GABA typically hyperpolarizes the postsynaptic resting membrane, which is why GABA's effect is called inhibitory. Neurotransmitters exert their effect by binding to receptors that

8. The quantitative description of the events associated with the action potential, by Alan Lloyd Hodgkin and Andrew Fielding Huxley, remains among the most significant conceptual breakthroughs in neuroscience. Their success story is also a reminder of the power of long-term collaboration between people with different but overlapping expertise. For a quantitative description of the action potential, see Johnston and Wu (1994).

reside in the membrane of the postsynaptic neuron. When activated, the receptors facilitate or suppress the kinetic activity of the Na^+, K^+, Cl^-, and Ca^{2+} channels so that the membrane potential will deviate from the resting voltage (see figure 6.3).[9] To define these respective events more clearly, we distinguish excitatory postsynaptic potentials (EPSPs; or currents, EPSCs) from inhibitory postsynaptic potentials (IPSPs; or currents, IPSCs). Compared to the fast action potentials, membrane potential changes associated with EPSPs and IPSPs are several-fold smaller in amplitude. However, they last for tens of milliseconds. This latter property is critical for understanding the generation of EEG activity.

Extracellular Currents

For the transmembrane potential to change in a given neuron, there must be a transmembrane current, that is, a flow of ions across the membrane. Opening of membrane channels (or, more precisely, an increase in their open state probability) allows transmembrane ion movement and is the source of ion flow in the extracellular space. The local field potential (i.e., local mean field), recorded at any given site in or outside the brain, reflects the linear sum of numerous overlapping fields generated by current *sources* (current from the intracellular space to the extracellular space) and *sinks* (current from the extracellular space to the intracellular space) distributed along multiple cells (figure 4.5). The low resistance or "shunting" effect of the extracellular fluid, the membranes of neurons, glia, and blood vessels, and the slow movement of ions attenuate current propagation in the extraneuronal space. Because the passive neuron acts as a capacitive low-pass filter, this attenuation is quite discriminative: it affects fast-rising events, such as the extracellular spikes, much more effectively than slowly undulating voltages.[10] As a result, the effects of postsynaptic potentials can propagate much farther in the extracellular space than can spikes. Furthermore, because of their longer duration, EPSPs and IPSPs have a much higher chance to occur in a temporally overlapping manner than do the very brief action potentials. Finally, EPSPs and IPSPs are displayed by many more neurons than are spikes because only a very small minority of neurons reach the spike threshold at any instant in time. For these reasons, the contribution of action potentials to the local field and especially to the scalp EEG is negligible.[11]

Excitatory currents, involving Na^+ or Ca^{2+} ions, flow inwardly at an excitatory synapse (i.e., from the activated postsynaptic site to the other parts of the cell) and outwardly away from it. The passive outward current far away from the synapse is referred to as a return current from the intracellular milieu to the extracellular

9. Besides the major neurotransmitters glutamate and GABA, several other subcortical neurotransmitters are known (see Johnston and Wu, 1994; see also Cycle 7).

10. A low-pass filter offers easy passage to low-frequency signals and difficult passage to high-frequency signals because the capacitor's impedance decreases with increasing frequency.

11. This is not necessarily the case under epileptic conditions, when neurons can synchronize within the duration of action potentials. The synchronously discharging neurons create local fields, known as compound or "population" spikes.

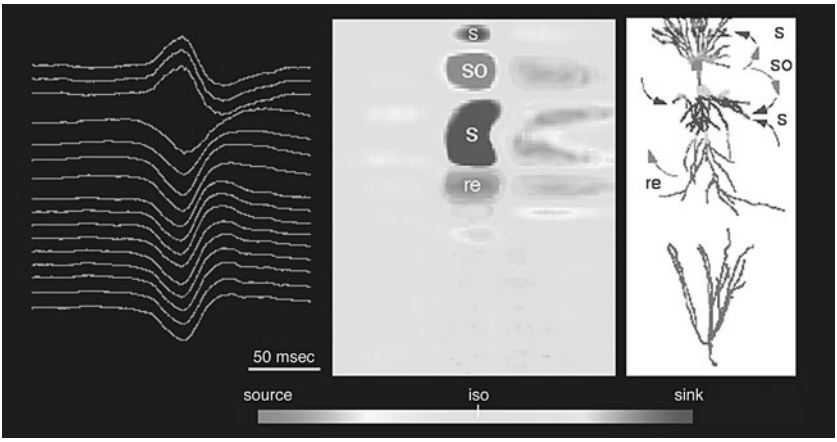

Figure 4.5. Generation of extracellular field potentials. Left: Spontaneously occurring field potential (sharp wave) recorded simultaneously in various layers of the hippocampus (CA1–dentate gyrus axis). The traces represent averages of 40 events. Middle: Current-source density map, constructed from the field potentials. Interpretation of the current sinks (s) and sources (so) is on the basis of anatomical connectivity, representing different domains of parallel-organized pyramidal cells and granule cells. Active currents are indicated on the right, and passive return (re) currents on the left, of the pyramidal neuron. The sinks in the dendritic layers are caused primarily by excitation from the upstream CA3 pyramidal cells, whereas the source around the soma reflects mainly inhibition, mediated by basket interneurons. Iso, isoelectric (neutral) state.

space. Inhibitory loop currents, involving Cl^- or K^+ ions, flow in the opposite direction. Viewed from the perspective of the extracellular space, membrane areas where current flows into or out of the cells are termed sinks or sources, respectively. The current flowing across the external resistance of the extraneuronal space sums with the loop currents of neighboring neurons to constitute the local mean field or local field potential (figure 4.5). In short, extracellular fields arise because the slow EPSPs and IPSPs allow for the temporal summation of currents of relatively synchronously activated neurons.[12]

Depending on the size and placement of the extracellular electrode, the volume of neurons that contributes to the measured signal varies substantially. With very fine electrodes, the local field potentials reflect the synaptic activity of tens to perhaps thousands of nearby neurons only. Local field potentials are thus the electric fields that reflect a weighted average of input signals on the dendrites and cell bodies of neurons in the vicinity of the electrode. If the electrode is small

12. This "classical" description of the origin of extracellular fields must be supplemented by the recent findings about the active properties of neurons (see Cycle 8; Llinás, 1988). Subthreshold oscillations, afterpotentials, Ca^{2+} spikes, and other intrinsic events also produce relatively long-lasting transmembrane events. The contribution of these nonsynaptic events to the local field potential can often be more important than the contribution of synaptic events (Buzsáki et al., 2003b).

enough and placed close to the cell bodies of neurons, extracellular spikes can also be recorded. Therefore, in such a small volume of neuronal tissue, one often finds a statistical relationship between local field potentials, reflecting mostly input signals (EPSPs and IPSPs), and the spike outputs of neurons. The reliability of such relationship, however, progressively decreases with increasing the electrode size, by lumping together electric fields from increasingly larger numbers of neurons. This is why the scalp EEG, a spatially smoothed version of the local field potential at numerous contiguous sites, has a relatively poor relationship with spiking activity of individual neurons.

In architecturally regular regions of the brain, such as the neocortex, the locations of the extracellular currents reflect the geometry of the inputs. Using several microelectrodes with regular distance from each other, one can calculate the density of the local currents from the simultaneously measured voltages, provided that information is available about the conductance of the tissue. Consider a distant current source relative to three equally spaced recording sites. Each electrode will measure some contribution of the field (due to the passive return currents that pass through the extracellular space) from the distant source. The voltage *difference* between two adjacent electrodes can determine the voltage gradient, that is, how fast the field attenuates with distance from the current source. Because the source is outside the area covered by the electrodes, the voltage gradient will be the same between electrodes 1 and 2 and between electrodes 2 and 3. Taking the difference between the voltage gradients, we get a value of zero, an indication that the measured field did not arise from local activity but was volume-conducted from elsewhere. In contrast, if the three electrodes span across a synchronously active afferent pathway, the voltage gradients will be unequal and their difference will be large, indicating the local origin of the current. By placing more microelectrodes closer to each other, we can more precisely determine the maximum current density and therefore the exact location of the maximum current flow.[13]

Unfortunately, from measuring the local current density alone, we have no way of telling whether, for example, an outward current close to the cell body layer is due to active inhibitory synaptic currents or if it reflects the passive return loop current of active excitatory currents produced in the dendrites. Without additional information that can clarify the nature of the current flow, the anatomical

13. Current density is is the current entering a volume of extracellular space, divided by the volume. The current flow between two sites (e.g., between recording electrodes 1 and 2 and between electrodes 2 and 3 in the example) can be calculated from the voltage difference and resistance using Ohm's law. The difference between these currents (i.e., the spatial derivative) is the current density. More precisely, the current density is a vector, reflecting the rate of current flow in a given direction through the unit surface or volume (measured in amperes per square meter for a surface and amperes per cubic meter for a volume). Current density depends on both the electric field strength and the conductivity (σ) of the brain. The conductance is a factor of both conductivity and the shape of volume. Conductivity is inversely proportional to resistivity. The average resistivity of white matter is ~ 700 Ω.cm, and that of gray matter is ~ 300 Ω.cm. The proportion of fibers therefore significantly affects tissue resistivity. For a thorough theoretical discussion of the current density method, I recommend Mitzdorf (1985) and Nicholson and Freeman (1975).

source remains ambiguous. The missing information may be obtained by simultaneous intracellular recording from representative neurons that are part of the population responsible for the generation of the local current. Alternatively, one can record extracellularly from identified pyramidal cells and interneurons and use the indirect spike-field correlations to determine whether, for example, a local current is an active, hyperpolarizing current or a passive, return current from a more distant depolarizing event. Taking these extra steps is worthwhile. The reward one obtains by pinning down the currents is crucial information about the anatomical source of the input to those same neurons whose output (i.e., spiking) activity is simultaneously monitored. Once information about both the input and output of a small collection of neurons working together becomes available, one may begin to understand the transformation rules governing their cooperative action. This approach is the next best thing to the ideal condition when all inputs (synapses) and the output of each cell could be monitored simultaneously and continuously.[14]

Functional Magnetic Resonance Imaging

Currently, the best-known noninvasive procedure for the functional investigation of the human brain is magnetic resonance imaging (MRI). The method is based on the detection and analysis of magnetic resonance energy from specific points in a volume of tissue. The MRI technique provides far better images than those the traditional X-ray and other scanning technologies. Hydrogen atoms of water represent tiny magnetic dipoles, which can align in an orderly way when placed inside of a very strong magnetic field. In practice, a short pulse of RF energy perturbs these tiny magnets from their preferred alignment. As they subsequently return to their original position, they give off small amounts of energy that can be detected and amplified with a "receiver coil" placed directly around the head. The injection of electromagnetic energy into a single plane is used to produce a slice through the brain volume. To produce consecutive brain slices, the head is advanced in small increments. Because gray matter and white matter contain different amounts of water, this difference generates a contrast between the surface of the neocortex and the underlying white matter and other areas of the brain that can be used to provide a detailed image of the brain. However, while the MRI method offers exquisite details about the structure of the brain, it does not tell us anything about neuronal activity.

As previously mentioned, active neurons consume a lot of energy, and in areas

14. Spike occurrences of in the vicinity of the cell body of the neurons reliably reflect their output messages. Unfortunately, no reliable methods exist to monitor all individual inputs to a single neuron simultaneously. Inputs can be estimated only by recording the local field potentials that reflect the spatially averaged activity of many neurons and inferring indirectly the mean input. Another, equally difficult approach is to monitor the spike output of the afferent neurons to the chosen recipient neuron and infer the input configurations from their spiking.

with high neuronal activity this results in a large difference between the concentration of the oxygenated hemoglobin in the arterial blood and the deoxygenated hemoglobin in the venous outflow. These local magnetic-field inhomogeneities can be assessed by the BOLD (blood-oxygenation-level–dependent) method. Functional MRI (fMRI), which uses the BOLD method, can measure neuronal activity indirectly.[15] Because of the unprecedented details of localized changes in the brain in response to various challenges and perturbations, the fMRI method has become the leading tool in cognitive science research. Nevertheless, as with any technique, fMRI has its limitations. The first limitation has to do with the general statement that "fMRI measures neuronal activity." Neuronal activity has numerous components, including intrinsic oscillations, EPSPs, IPSPs both in principal cells and in inhibitory interneurons, action potential generation and propagation along the axon, and release, binding, reuptake, and reprocessing of the released neurotransmitter. Which of these processes, alone or in combination, are responsible for the changes in BOLD has yet to be worked out. Without such crucial information, it is not possible to conclude whether an increase in BOLD results from increased firing of principal cells or interneurons or increased release of neurotransmitter from afferents whose cell bodies are outside the area with increased BOLD signal.

The second problem arises from the neurophysiological observations that numerous brain operations are brought about by changing the firing patterns of neurons without any change in the rate of postsynaptic potentials or alteration of neuronal firing rates (I provide some examples in Cycles 8, 9, and 12). For example, recognition or recall of the correct and incorrect information may use different sets of neurons but engages those neurons with the same magnitude of activity. Thus, fundamentally different cognitive operations in the same structures can be generated with the same amount of energy, with no expected change in BOLD. This reverse engineering problem is, of course, identical to that of the EEG and MEG. Thus, with the exception of significantly improved spatial resolution, one cannot expect more from fMRI than from EEG measurements.

The third technical drawback of fMRI is its slow temporal resolution. Not only is the blood-flow response delayed about half a second after neuronal activation, but also the second-scale temporal resolution of the BOLD imaging method is excessively long for assessing spatiotemporal evolution of neuronal activity across brain domains. As discussed in Cycle 2, activity can get from any structure to just about any other structure in the brain by crossing just five to six synapses within a second. Even if only a few areas show increased BOLD activity, we have no knowledge about the temporal sequence of their activation, a critical issue for

15. During the late 1980s, Seiji Ogawa, then at Bell Labs in Murray Hill, New Jersey, noted that cortical blood vessels became more visible as blood oxygen was lowered. From these initial observations, he concluded that the local magnetic field inhomogeneities can be used to assess neuronal activity, and termed his invention the blood-oxygenation-level–dependent (BOLD) method (Ogawa et al., 1990). For a brief discussion on the complex origin of BOLD, I suggest Logothetis (2003), Logothetis et al. (2001), and Raichle (2003).

understanding how the information is processed. Understanding the neuronal mechanisms that give rise to overt and cognitive actions requires method(s) at the temporal resolution of behavior.

Positron Emission Tomography

Another important research tool for visualizing brain function is positron emission tomography (PET). A major advantage of PET is that it provides information about the use and binding of specific chemicals, drugs, and neurotransmitters in the brain. To obtain a PET scan, the subject either inhales or receives an injection of a very small amount of a radiolabeled compound, which then accumulates in the brain. As the radioactive atoms in the compound decay, they release positively charged positrons. When a positron collides with a negatively charged electron, they are both annihilated, and two photons are emitted. The photons move in opposite directions and are detected by the sensor ring of the PET scanner. Reconstruction of the three-dimensional paths of the particles provides information about the maximum accumulation or metabolism of the radiolabeled isotope. Both the spatial and temporal resolutions of PET are inferior to fMRI.

Let me pause here to add a few important details regarding all of these advanced imaging methods. A single MEG, PET, or fMRI device weighs several tons. Because the subject's head must be immobilized for brain scanning, these methods are not practical for the examination of behavior-generated brain changes in the most frequently used small laboratory animals, such as rats and mice. More important, even the combined, simultaneous application of these methods falls short of the goal of explaining how neurons and neuronal assemblies make sense of the world, generate ideas and goals, and create appropriate responses in a changing environment. In the brain, specific behaviors emerge from the interaction of neurons and neuronal pools. Although EEG, MEG, fMRI, PET, and related methods have opened new windows on brain function, in the end all these indirect observations need to be reconverted into a common currency—the format of neuronal spike trains—to understand the brain's control of behavior.

Increasing Spatial and Temporal Resolution: Optic Methods

To date, the best spatial resolution of neuronal activity is provided by optical methods. By viewing through a microscope, light intensity or color changes can be monitored at the micrometer scale, and at the same time, large two-dimensional areas can be observed, just like watching a movie screen. The trick is to extract functional information from the optically detected signals. The most prominent pioneer in this field has been Amiram Grinvald of the Weizmann Institute of Science in Rehovot, Israel. Working first with invertebrates and later in the

monkey visual cortex, Grinvald noticed that neuronal activity affects the optical properties of brain tissue, which can be conveniently monitored by photon-detecting arrays or sensitive cameras. His method is known as intrinsic optical imaging, because it is based on the light-reflecting/absorbing properties of the intact brain tissue. All that is needed is a very sensitive, fast camera to be able to watch the brain in action. Unfortunately, interpretation of the obtained images in terms of neuronal function is even more difficult than in the case of fMRI. The potential sources for these activity-dependent intrinsic signals are numerous and include changes in the physical properties of the tissue itself, which affect light scattering, or changes in the absorption, fluorescence, or other optical properties of various molecules having significant absorption or fluorescence, for example, hemoglobin or cytochromes.[16]

The temporal resolution of the intrinsic imaging method can be significantly improved by using compounds whose optical properties can be altered by some brain mechanisms. For example, voltage-sensitive dyes bind to the external surface of the neuronal membrane and act as molecular transducers to transform changes in membrane potential into optical signals. Optical imaging with voltage-sensitive dyes and fast photodetecting devices permit the visualization of neuronal activity with improved temporal resolution and a spatial resolution of approximately 100 micrometers. This method combines the advantageous features of surface local field potential recordings with high spatial resolution. There are a few methodological caveats, however. The dye has to be applied physically to the surface of the brain, making prolonged and repeated observations difficult. Single cells cannot be identified, and more critically, input and output actions of the neurons cannot be separated; thus, their contribution to the transfer of information can be inferred by indirect means only or from a combination with other methods. Finally, because the optical method works much like our video cameras, it allows for the observation of surface events only, and it is hard to figure out what happens inside the neocortex or in deeper brain structures.[17]

Penetration into deeper layers of the neocortex is possible with another innovation, known as two-photon or multiphoton laser scanning microscopy (2-PLSM or m-PLSM).[18] Only three things are needed for this powerful method to work: extremely powerful laser pulses in the 700–900 nanometer range (deep red to infrared), molecules that change their fluorescence relevant to some physiological

16. Hemoglobin is a protein that binds oxygen. Cytochromes are energy-producing enzymes in the inner mitochondrial membrane that catalyze the reaction between ferrocytochrome c and oxygen to yield ferricytochrome c and water. It is associated with the pumping of protons and the resultant phosphorylation of ADP to ATP, a molecule in great demand for energy. The high metabolic rate of neurons explains their strong cytochrome activity. Fast-firing interneurons have a particularly high density of cytochromes (Gulyás et al., 2006); therefore, they may bias the optical images.

17. For an overview of the fast imaging methods with voltage-sensitive dyes, see Grinvald and Hildesheim (2004). In principle, optical fibers can be lowered into the depth of the brain. However, the spatial coverage of this invasive modification is limited.

18. Winfried Denk, then a graduate student at Cornell University in New York, James Strickler, and their adviser, Watt W. Webb, constructed the first 2-PLSM in 1990 (Denk et al., 1990).

activity, and the ability of the microscope to collect the emitted fluorescence photons for producing a three-dimensional image. Very high energies are needed for two- or multiphoton interactions with the fluorescing target. When this occurs, the individual energies of the photons combine, and the cumulative effect is the equivalent of delivering one photon with twice the energy (in the case of two-photon excitation) or three times the energy (in three-photon excitation). High-wattage lasers can easily fry the brain instantaneously. To avoid such an undesirable effect, the laser beams are pulsed so that only very short, 100 femtosecond long pulses penetrate the brain. The scanning beam is a moving point, like the cathode ray in the TV screen tube; therefore, the brain targets are affected only at the time the beam moves across them. The 2-PLSM produces high-resolution, three-dimensional pictures of tissues with minimal damage to living cells.[19]

Most current functional measurements with 2-PLSM investigate intracellular calcium changes, simply because effective fluorescent sensors are available for this ion. Methods for the direct detection of action potentials and other functional indices are being developed. The optical imaging methods will fully reach their potential when combined with the rapidly evolving tools of molecular biology for the creation of function-sensing fluorescent markers. Some further practical problems, such as the trade-off between temporal and spatial resolution, can be addressed and perhaps resolved. However, obtaining images in deep layers of the neocortex or structures below the cortex remains a challenge even in small animals. In the meantime, alternative methods are needed to monitor the cooperative action of individual neurons.

Recordings from Single Neurons *In Vitro*

Neurons are complex devices. Understanding the biophysical properties of individual neurons would greatly enhance understanding their collective behavior in networks. Characterization of individual neurons is especially critical in brain regions built from a variety of different neuron types. Most of our knowledge about the biophysical properties of neurons is derived from experiments carried out in brain slice preparations *in vitro.* Although the brain slice method compromises brain circuits, it provides unprecedented spatial resolution, precision, and pharmacological specificity for the examination of the biophysical and molecular properties of the cell membrane. Brain slices allow recording from local neural circuits,

19. After moving to the Bell Laboratories, Denk and his colleagues David Tank, Karel Svoboda, and Rafael Yuste provided images of neurons from the living brain with details that rivaled those visualized in fixed tissue and coupled these detailed images to brain function (Denk et al., 1996). Recognizing that the most meaningful test of any hypothesized brain mechanism is behavior, they constructed a miniaturized prototype of the 2-PLSM that can potentially be carried by a small animal (Helmchen et al., 2001).

with the advantages of mechanical stability, direct visualization of neurons, and the experimenter's control over the extracellular environment.[20] Depending on the age of the animal, the thinly cut sections of the brain, placed in a humidified, temperature-controlled dish and perfused with oxygenated cerebrospinal fluid, can be kept alive for several hours. Using a microscope and an infrared camera, the outlines of individual neurons can be visualized. In case of very young animals, whole pieces of brain structures, for example, the hippocampus, can be kept alive *in vitro*. Various drugs and electrolytes can be perfused or applied locally under visual control.[21]

The popularity of the brain slice method was catalyzed by another groundbreaking innovation, the patch-clamp technique, introduced by Erwin Neher and Bert Sakmann of the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. The key invention in patch-clamp recording is the use of a pipette with a finely polished end. The pipette can be attached gently to the cell membrane, and by applying negative pressure through the pipette, a piece of the cell membrane, the patch, is "sucked" into the pipette. The result is that the membrane attached to the pipette becomes mechanically and electrically isolated ("sealed") from the surrounding extracellular fluid. By applying a short pulse of low pressure through the pipette, the patch can be broken and a direct junction between the

20. Brain slices are used for a wide variety of studies, including synaptic plasticity and development, network oscillations, and intrinsic and synaptic properties of anatomically defined neurons. The *in vitro* slice preparation was introduced by Yamamoto and McIlwain (1966). Soon after it was adopted for the physiological examination of the hippocampus in Per Andersen's laboratory in the Institute of Physiology, Oslo, Norway in the 1970s, it became the method of choice for biophysical and pharmacological investigation of single neurons (see Skede and Westgaard 1971).

21. Khalilov et al. (1997). In addition to studying single neurons, brain slices have been used extensively to study the emergence of network oscillation. A variety of oscillatory patterns, reminiscent of those in the intact brain, have been replicated in brain slices despite the fact that in these reduced preparations only a small fraction of the *in vivo* network is present. Do these *in vitro* models faithfully represent the rhythms they intend to mimic? If so, the model is of great value, because the reduced preparations exclude a large number of variables that are uncontrollable in the intact brain and allow for systematic changes of various parameters that are critical for the emergence, maintenance, and termination of the oscillation. Reduction of the parameter space, in turn, allows for the construction of computer models for the identification of the necessary and sufficient conditions underlying various aspects of the oscillations (Traub et al., 1999; Destexhe and Sejnowski, 2001, 2003). The final and most important step in this "reverse engineering" strategy is the comparison of the *in vitro* and *in silico* (i.e., computational modeling) engineered rhythms with those of the intact brain. It is this stage that should address the important question of whether the evoking conditions in the reduced system are in fact present in the intact brain and to identify the similar and dissimilar aspects of the observed and created oscillations. This process should also identify features of the oscillation that cannot be reproduced in the model and should thus point to the need for larger circuits and more complex interactions than are offered by the model. Unfortunately, *in vivo* and *in vitro* experiments and computational modeling are rarely done in the same laboratory. As a result, models too often claim too much. On the other hand, critical details are often not accessible through the *in vivo* approach. It is fair to say that, to date, oscillations that have been reproduced and studied with excruciating details *in vitro* and in models are best understood.

inside of the neuron and the electrolyte solution in the pipette is established.[22] Any current waveform can be applied, and relatively large molecules can be "washed" into the neuron through the pipette. Alternatively, a piece of a membrane, sealed to the pipette tip, can be torn away, and the channels inside the membrane piece can be studied electrically and pharmacologically. Patch-clamp experiments performed in the *in vitro* slice preparation have provided unprecedented details about the active properties of neurons and important insights into the mechanisms of network oscillations.[23]

Extracellular Recordings from Single Neurons

Because action potentials produce large transmembrane potentials in the vicinity of the cell body, the occurrence of the spike can be sensed by a conductive microelectrode positioned near the cell body of the neuron by means of a precision mechanical drive. The voltage-sensing microelectrode, in essence, is a very sharp insect pin, insulated except for the last few micrometers of the tip. The closer the recording tip is to the neuron, the louder one can hear the action potentials, provided that the amplified voltage is connected to a loudspeaker. With some maneuvering by a mechanical micromanipulator device, the signal can be maximized so that one neuron's "voice" stands out from the others, a procedure called cell "isolation."[24] If other active (spiking) neurons are in the vicinity of the tip, the electrode records from all of them. Because neurons of the same class generate virtually identical action potentials, the only way to identify a given neuron from

22. The membrane can be penetrated by sharp glass electrodes, as well. This sharp electrode approach has been used successfully for intracellular recordings of neurons for many years. However, because its tiny tip cannot be easily visualized under the microscope, the sharp electrode methods became less popular in *in vitro* experiments.

23. The patch-clamp method in fact refers to four different methods. (1) The most popular version is the whole-cell method, typically patching the cell body. A major advantage of the whole-cell method is the very low access resistance between the electrode content and the cytosol. This allows "clamping" the membrane voltage to any arbitrary value, e.g., reversal potential of chloride or sodium, and measuring the current flowing through the membrane. (2) The "cell-attached" method is basically an extracellular method. A difference from other extracellular methods is that the tip of an electrode is attached tightly to the membrane and the inside of the pipette is isolated from the extracellular environment electrically (a "gigaohm seal" is established). This feature prevents signals from other neurons from interfering with the activity of the recorded neuron. The polished pipette method is also useful to investigate ion channels in excised patches of the membrane without the influence from the rest of the neuron. (3) In the inside-out configuration, the outer membrane surface is facing the pipette's orifice whereas (4) in the outside-out configuration it is the inner membrane surface. Prior to the patch-clamp method, neurons had been impaled with a sharp glass electrode successfully for many years. The disadvantages of glass pipettes are their small size and the high resistance of their tips, which makes delivering chemicals and large currents more difficult.

24. The tungsten extracellular electrode method was introduced by Hubel (1957) for the exploration of single neuronal responses in the visual cortex. The single-cell recording method has generated a wealth of information about a wide range of issues, including sensory representation, short-term memory, and motor organization.

extracellularly recorded spikes is to move the electrode tip closer to its body (< 20 micrometers in cortex) than to any other neuron. The much larger spike from the closest cell, relative to the spikes of more distant neurons, is often sufficient to reliably monitor the output of a single cell. However, being very close to a neuronal membrane with a sharp tip can be dangerous. Very small movements of the brain, due to pulsation of the vessels, breathing-related shifts, or head position changes can affect the relationship between the electrode tip and the neuron. The neuron is easily injured, and perturbation of its immediate environment can affect its firing pattern. To record from another neuron with certainty, yet another electrode is needed.

Triangulation of Neurons by Tetrodes

Triangulation of biological voltage sources began with the studies of the heart, and the triangulation method has remained a routine method in the evaluation of the electrocardiogram (EKG). The heart is massively connected torus of muscle cells and produces a huge electrical signal (in the millivolt range) compared to the brain. Created by placing just four electrodes on the left foot, right and left arms, and chest, the heart "tetrode" is a pretty efficient routine clinical tool for the localization of the anatomical sources of the components of the EKG (figure 4.6). For more precise localization, many more electrodes are used.[25] The triangulation method, of course, should work for the localization of any stationary dipole, including action potentials generated by neurons. The idea of triangulation for neuron separation was first introduced by John O'Keefe and Bruce McNaughton, at University College, London. Their first sensor consisted of two 25-micrometer-long insulated wires twisted together, fittingly called the "stereotrode," followed by the four-wire version called a "tetrode" (figure 4.6, bottom).[26] A typical tetrode consists of four thin wires (12–15 micrometers in diameter each) glued together in a bundle. With only one electrode tip, signals from many neurons that are located at the same distance from the tip in a sphere provide similar amplitude spikes, making single-cell isolation difficult. Thus, we may hear and see many neurons, but we cannot tell them apart. With two closely spaced electrodes, the ambiguity can be decreased to neurons in a plane, and with three electrodes to neurons sitting in a line. If a fourth electrode is placed in different plane from the

25. Willem Einthoven, whose string galvanometer was used to detect EEG signals by Berger, worked out the first diagnostic rules of heart signals on the basis of triangulation. The Einthoven triangle is an imaginary equilateral triangle with the heart at its center, its equal sides representing the three standard limb leads of the electrocardiogram (see figure 4.6, top right). In the electrocardiogram, at any given instant the potential of any wave between two limbs is equal to the sum of the potentials in leads obtained from the other limbs.

26. McNaughton et al. (1983a) and Gray et al. (1995). The tetrode catapulted into its present fame after Wilson and McNaughton (1993) recorded from more than 100 neurons in a freely moving rat, using 12 movable tetrodes.

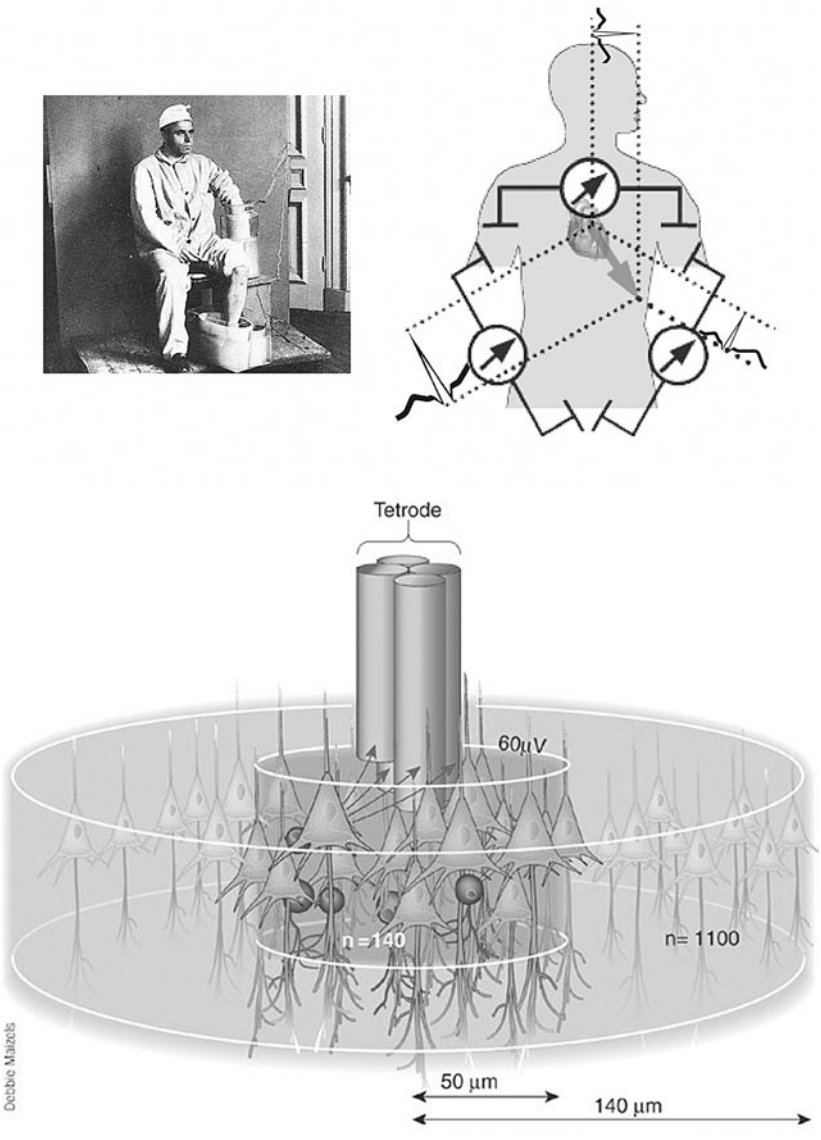

Figure 4.6. Source localization by triangulation. For determining the heart's electrical axis, voltage measurements are made between the right and left arms, right arm and left leg, and left arm and left leg (top right). Photograph (top left) illustrates Willem Einthoven's "electrodes": the subject places an arm and a leg in salt water connected to a galvanometer. From the voltage deflections in each measurement, the voltage vector can be calculated. Bottom: Triangulation of the three-dimensional position of neurons by "tetrode" measurements. The voltage differences between the wires of the tetrodes of the recorded spikes from individual neurons allow the calculation of the unique position of each neuron. Modified, with permission, from Buzsáki (2004).

other three, the spatial position of each neuron in the line, in principle, can be separated by triangulation.

Wire tetrodes have numerous advantages over sharp-tip single electrodes. First, they provide recording stability. The thin wires are flexible and can move together with the brain to some extent. This is why recordings of neurons in deeper structures are more stable than those of neurons in, for example, the superficial layers of the cortex. Because the recording tip need not be placed in the immediate vicinity of the neuron, small movements of the tetrode are not as detrimental as would be the case of a sharp tip touching the neuron. Tetrodes are especially useful in areas with a high packing density of neurons, where isolation of individual neurons from nearby peers is difficult with single wires. Under ideal conditions, a tetrode can record up to 20 well-isolated neurons.

Cortical pyramidal cells generate extracellular fields that flow mostly parallel to their somadendritic axis. For this reason, the action potentials can be detected several hundred micrometers from the soma, in the proximity of thick apical dendrites. The lateral spread of current is more restricted. Nevertheless, tetrodes can "hear" pyramidal cells as far away as 140 micrometers lateral to the cell body, although the extracellular spike amplitude decreases rapidly as a function of distance from the neuron. A cylinder with a radius of 140 micrometers contains approximately 1,000 neurons in the rat cortex, which is therefore the upper limit of the theoretically recordable cells by a single electrode. Yet, in practice, only a small fraction of these neurons can be reliably separated (up to 20 neurons under ideal conditions).[27] The remaining neurons may be damaged by the blunt end of the closely spaced wires or remain undetected with currently available spike-sorting algorithms. Thus, there is a large gap between the number of routinely recorded and theoretically recordable neurons. To monitor another dozen or so neurons, another tetrode is needed. Because inserting wires in the brain is an invasive procedure, recording from large numbers of neurons is possible only at the expense of extensive cell damage.

High-Density Recordings with Silicon Probes

An ideal recording electrode has a very small volume, so that tissue injury is minimized. On the other hand, recording from many neurons with wire electrodes requires large numbers of wires with consequent tissue damage. Obviously, these competing requirements are difficult to meet. A wire electrode has only one useful site, the conductive tip; the rest is just conduit and inconvenient bulk. To increase the number of useful recording sites without increasing the volume of the

27. Henze et al. (2000a) determined the relationship between the distance of the extracellular electrode from the spiking neuron and the amplitude of the recorded spikes by monitoring the same neurons both intracellularly and extracellularly in the intact hippocampus. For modeling extracellular spike waveforms, see Gold et al. (2005). A concise overview of the extracellular recording methods is Nádasdy et al. (1998).

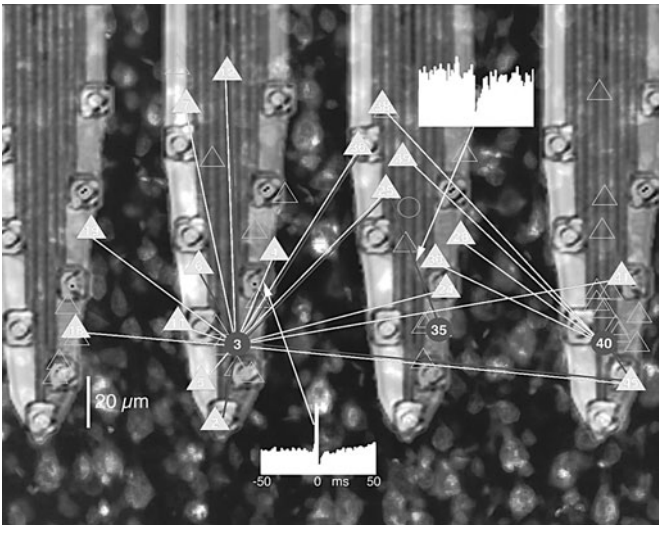

Figure 4.7. Functional connectivity within local microcircuits of the somatosensory cortex of the rat. Synaptic connections between participating pyramidal cells (triangles) and putative interneurons (circles) can be determined by their temporal relationship. For example, decreased discharge of a partner neuron immediately after the spike of the reference cell (time zero in the upper white histogram) reveals the inhibitory nature of the reference neuron. Conversely, a consistent, short-latency discharge of the partner neuron after the reference spike (lower histogram) indicates the excitatory nature of the reference cell. Modified, with permission, from Barthó et al. (2004).

electrode, Kensall Wise at the University of Michigan devised multisite recording probes, using silicon "chip" technology. These microelectromechanical system (MEMS)–based recording devices can reduce the technical limitations inherent in wire electrodes because with the same amount of tissue displacement, the number of monitoring sites can be substantially increased. These silicon devices share the advantages of tetrode recording principles, yet they are substantially smaller in size. At the current level of development, multishank silicon probes can record from as many as 100 well-separated neurons. Importantly, the geometrically precise distribution of the recording sites also allows for determination of the spatial relationship and the functional connectedness of the isolated single neurons (figure 4.7). This feature is a prerequisite for studying the spatiotemporal representation and transformation of inputs by neuronal ensembles.[28]

28. Wise and Najafi (1991). A major advantage of silicon probes is that with integrated chip technology virtually any two- and even three-dimensional arrays can be fabricated, which is a highly desirable feature for the exploration of local networks. In addition to recording from multiple sites, silicon electrodes can use on-chip amplification, filtering, and time-division multiplexing as well as programmed microstimulation through the recording sites and, potentially, real-time signal processing (Olsson et al., 2005). Such a brain–chip interface may allow for reciprocal interactions with the brain, paving the way for fully implantable neural prosthetic devices.

Isolation and Identification of Neurons by Extracellular Signatures

An indispensable step in spike-train analysis is the isolation of single neurons on the basis of extracellular features. Spike-sorting methods fall into two broad classes. The first class attempts to separate spikes on the basis of amplitude and waveform variation, on the assumption that neighboring neurons generate distinct spike features. This assumption is difficult to justify in most cases because similar neurons at similar distances from the recording electrode tip generate nearly identical waveforms. As a result, these neurons may be inadvertently combined as if the spikes were generated from a single neuron. The converse problem also occurs: the same neuron can generate different waveforms, depending on firing rates, the magnitude of somadendritic propagation of spikes, and activation of various channels in different states. The consequence of these wave shape variations is that spikes generated by the same neuron under different conditions will be classified by the wave shape discrimination method as if the spikes with different forms emanated from different cells.

The second general approach, the triangulation method discussed above, is based on the tacit assumption that the extracellularly recorded spikes emanate from point sources rather than the complex geometry of neurons. This is obviously a simplistic notion, because every part of the neuronal membrane is capable of generating action potentials. The extent of the somadendritic back-propagation of the action potential varies as a function of the excitatory and inhibitory inputs impinging on the neuron. Because the extracellular spike is a summation of the integrated signals from both soma and large proximal dendrites, the extracellularly recorded spike parameters depend on the extent of spike back-propagation and on other state- and behavior-dependent changes of the membrane potential. These changes can affect the estimation of the neuron's virtual "point source" location and may place the same neuron at different locations, resulting in errors of spike assignment to neurons.[29] Another problem with the point-source assumption for action potentials is that the somatic origin is not always resolvable with distant recording sites. For example, in the neocortex, extracellular spikes can be recorded from the large apical shaft of layer 5 pyramidal neurons as far as 500 micrometers from the cell body. As a consequence, a single electrode tip, placed, for example, in layer 4, can record equally well from layer 4 cell bodies or apical dendrites of deeper neurons. These sources of unit sorting errors can be reduced by recording at multiple sites, using silicon probes, placed parallel to the axodendritic axis of the neurons.[30]

29. The spike amplitude variation is most substantial during complex spike-burst production, when the amplitude of the extracellular spikes may decrease as much as 80 percent, associated with changes in other waveform parameters.

30. The amplitude and waveform variability of the extracellularly recorded spike is the major cause of unit isolation errors. Triangulation methods visually analyze two-dimensionally projected datasets one at a time. With multisite-recorded data, successive comparisons of the various possible projections generate cumulative errors of human judgment. Cumulative human errors can be reduced

Separation of Neuronal Classes

Because brain networks consist of several neuronal classes, each with a specific computation task, their separation on the basis of extracellular features is highly desirable. Several features of the extracellular spikes may assist with this process, including spike duration, firing rate and pattern, spike waveform, and the relationship to network patterns. In the cortex, the most important step is the separation of pyramidal cells and inhibitory interneurons. This step, in itself, is difficult, and progress depends on the successful combination of extracellular and intracellular or other anatomical labeling methods that allow verification of the recorded neuron types. Separation of the different principal and inhibitory neuronal subclasses is a further challenge but a necessary requirement for the understanding and interpretation of assembly cooperation.[31]

Analyses of Brain Signals

Because neuronal signals have two fundamental appearances, the continuous membrane potential and field potentials (or analog signals) and the discrete (or digital) action potentials, their analyses require a combination of methods applicable for both continuous and point processes. Irrespective of the nature of the observed signal, brain activity has multiple frequencies and evolves over time. Therefore, the most appropriate method for analyzing brain signals would be a "time–frequency analysis" algorithm that would provide a perfect description of changes in all frequencies as a function of time. However, frequency and time cannot be mixed; mathematically speaking, they are orthogonal. The implication is that there is no concept of time in the frequency domain, and conversely, there is no concept of frequency in the time domain. This counterintuitive relationship explains why the two major classes of analytical tools that are used for the analyses of brain signals are called "frequency domain" and "time domain" methods.

Suppose that we would like to "analyze" speech without knowing what information we are exactly looking for. One approach can characterize the distribution of frequencies in spoken speech. Because consonants and vowels are composed of characteristic constellations of frequencies, and because the probability distribution of the individual consonants and vowels in language is quite different, some frequencies will dominate the speech frequency landscape. To make sure that all

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by semiautomatic clustering methods of high-dimensional data. A further difficulty is that no independent criteria are available for the assessment of omission and commission errors of unit isolation. As a result, improvement of spike-sorting algorithms is not guided by objective measures. In the absence of quantitative criteria for unit isolation quality, interlaboratory comparison is difficult and is often a source for the controversy in data interpretation. This area of research can strongly benefit from future technical improvements (Henze et al., 2000a; Barthó et al., 2004; Buzsáki, 2004).

31. The combination of the various technical approaches proved successful for the classification of some interneuron classes in the hippocampus (Csicsvari et al., 1999; Klausberger et al., 2003, 2004).

sounds are sampled representatively, long epochs are needed for the analysis. Alternatively, we can pick a characteristic frequency distribution pattern, determined in a short time epoch, and examine its distribution over time. Obviously, neither method alone can reveal the information-encoding scheme of speech. A frequency domain graph shows only how much of the signal lies within each given frequency band over a range of frequencies, whereas a time domain display shows only how a piece of the signal changes over time. EEG, MEG, and even spike-train signals have both time- and frequency-domain representations that are not fundamentally different from the example of speech. Understanding the coding ability of time-evolving neuronal signals, therefore, also requires appropriate methods.

Because brain signals contain multiple frequency components, their relationship can be quantified using frequency domain methods. The complex EEG or MEG waveform can be reproduced by an appropriate combination of sine waves. This method is similar to the trick used by electronic synthesizers that can make convincing acoustical forgeries of everything from trombones to harps. It is done by a mathematical process called Fourier synthesis, named after the French mathematician Joseph Fourier.[32] The reverse process, called Fourier analysis, takes the complex EEG or MEG signal and decomposes it into the sine waves that make it up. After the signal is decomposed into sine waves, a compressed representation of the relative dominance of the various frequencies can be constructed. This frequency versus incidence illustration is known as the *power spectrum.* The Fourier method transforms the signal, defined in the time domain, into one defined in the frequency domain. Although this representation ignores the temporal variation of the EEG signal, it provides a quantitative answer regarding the power relationship between the frequencies.

Determining the frequency from any continuous pattern requires making measurements of time intervals before doing any calculation. However, in complex waveforms such as the EEG, where multiple frequencies are simultaneously present, it is often unclear where the intervals to be measured begin and end, that is, where the analyzed epochs should be. The theory of Fourier transform assumes that the signal is analyzed over all time—an infinite duration. This restriction suggests that the standard Fourier analysis is not well suited to describing time-transient changes in "frequency content" because the frequency components defined by the Fourier transform require infinite time support.[33]

32. Jean Baptiste Joseph Fourier was as impatient as any self-respecting young scientist. In a letter that he sent together with a paper on algebra to C. Bonard, he complained: "Yesterday was my 21st birthday; at that age Newton and Pascal had already acquired many claims to immortality." Fourier's immortal fame is mainly due to the method he introduced, the Fourier transform, which expresses a waveform as a weighted sum of sines and cosines. In essence, it decomposes or separates a waveform or function into sinusoids of different frequencies that sum to the original waveform. It identifies or distinguishes the different frequency sinusoids and their respective amplitudes. The Fourier transform of the autocorrelation function is the power spectrum and is illustrated by a plot of $P(f)$ as a function of f.

33. The temporal resolution of the serial Fourier transform display assumes that the selected segments are stationary. E.g., when low frequencies are also of interest (e.g., 1 hertz), then the temporal window of analysis must be slow enough ($> 2 \times 1$ second). For a short overview of spectral methods of EEG signals, see Muthuswamy and Thakor (1998).

A practical "solution" to the time versus frequency orthogonality issue is the short-time Fourier transform, which attempts to quantify the frequency content changes over time. In this modified analysis, the brain signal is divided into multiple short epochs, and the Fourier transform is calculated for each epoch. The successive spectra can display the evolution of frequency content with time. The short-time Fourier transform can be viewed as a compromise of joint time–frequency analysis. The use of a wide temporal window will give good frequency resolution but poor time resolution, whereas the use of a narrow window will give good time resolution but poor frequency resolution. Accepting this compromise, these modified methods can analyze sequential short epochs, and the frequency structure can be displayed as a function of time (figure 4.8).

Another popular way of analyzing short-time segments of selected EEG patterns is called "wavelet" analysis. The wave refers to the fact that this function is

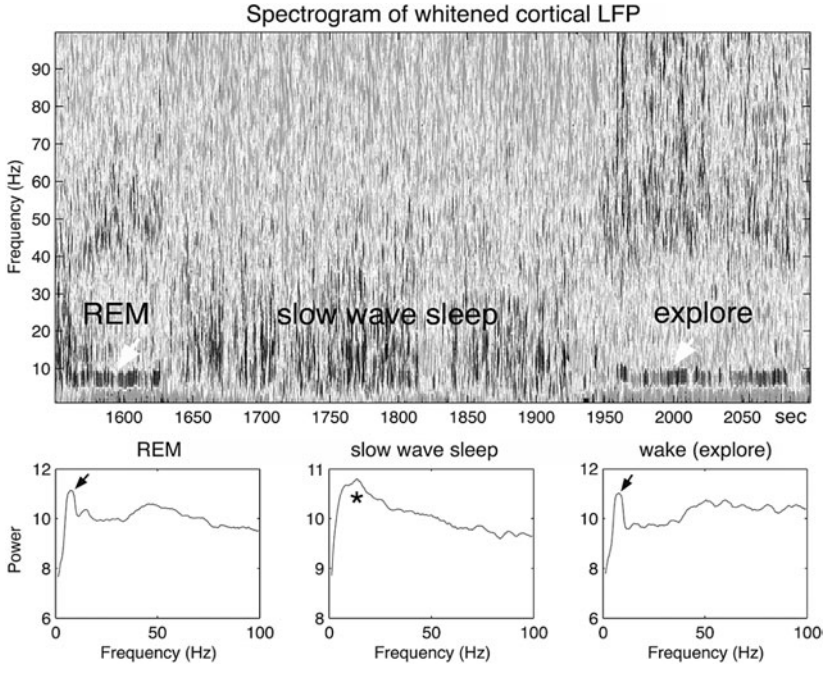

Figure 4.8. Frequency spectral dynamics of an EEG. Top: Gray-scale–coded power of neocortical local field potential in the rat during REM (rapid eye movement) sleep, slow wave sleep, and waking exploration. Arrows indicate volume-conducted theta frequency (7–9 hertz) oscillation from the underlying hippocampus. Bottom: Fourier spectra of lumped epochs. The asterisk indicates the power peak in the sleep spindle band (12–18 hertz). Note the distinct theta and gamma (40–90 hertz) frequency power increase during REM sleep and waking. The spectra have been "whitened" by removing the 1/*f* correlated power (see Cycle 5 for explanation of this term). LFP, local field potential. Figure courtesy of Anton Sirota.

oscillatory; the diminutive form refers to the fact that this (window) function is of finite length or a fast-decaying, oscillating waveform. The wavelet transform refers to the representation of a signal in terms of a finite length. Rather than analyzing the distribution of all frequencies, the wavelet transform first selects a "frequency of interest."[34] Any arbitrary waveform can serve as a "prototype" whose consistent appearance can be quantified. Therefore, all wavelet transforms may be considered to be forms of time–frequency representation.[35]

Analysis in the time domain is usually performed by temporal correlation functions. Correlating a signal with itself is called autocorrelation, which can reveal repetitive components in the signal. Because different sorts of signals have distinctly different autocorrelation functions, these functions can be used to tell signals apart. For example, random noise is defined as uncorrelated because it is similar only to itself, and any small amount of temporal shift results in no correlation with the unshifted signal at all. In contrast, oscillating signals go in and out of phase when shifted in time. The autocorrelation function of a periodic signal is itself a periodic signal, with a period identical to the original signal. Therefore, autocorrelation is an effective method for revealing periodic function in a signal. Correlation methods are also often used to assess the similarity between two signals. When two signals are similar in shape and are in phase (i.e., "unshifted" with respect to each other), their correlation is positive and maximum. The same signals out of phase will provide a negative maximum correlation. As one signal is shifted with respect to the other and the signals go out of phase, the correlation decreases. Correlating a signal with another, that is, computing their cross-correlation, is a powerful method for detecting a known reference signal in noise or the directional connectedness of neuron pairs (figure 4.7).

Forms of Oscillatory Synchrony

There are numerous ways to affect oscillators, and the mechanisms that modify them do not even have a standardized taxonomy. Some of the terms have agreed mechanisms within one discipline but are used differently in another. Here are definitions of a few terms as they are used in neuroscience and in the neurocomputation literature. *Mutual entrainment* refers to a measure of stability of two or more oscillators that they would not have on their own. Mutual feedback is the key to entrainment of oscillators of various frequencies and stabilities. For example, when multiple single-cell oscillators with different intrinsic frequencies are

34. Wavelet transforms are broadly classified into the discrete wavelet transform and the continuous wavelet transform. The discrete transform uses a specific subset of all scale and translation values, whereas the continuous transform operates over every possible scale and translation.

35. "The wavelet transform replaces one single, poorly behaved time series with a collection of much better behaved sequences amenable to standard statistical tools" (Percival and Warden, 2000). Although both wavelet and Hilbert transformation methods have become widely used recently, these methods are formally (i.e., mathematically) identical with the Fourier transform (Bruns, 2004).

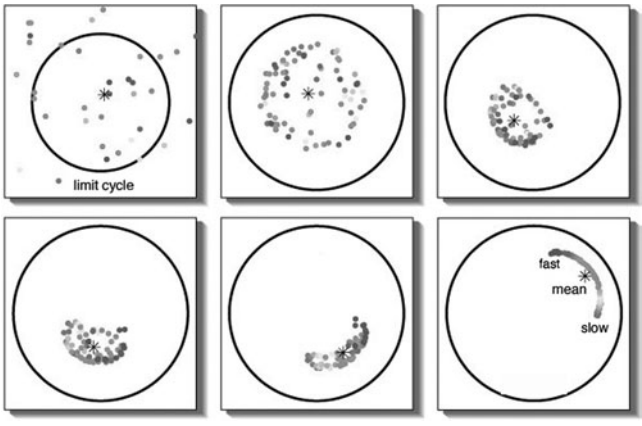

Figure 4.9. Collective synchronization of multiple oscillators. The state of each oscillator is represented as a dot in the complex plane. The amplitude and phase of the oscillation correspond to the radius and angle of the dot in polar coordinates. Gray scale codes the oscillators' natural frequencies. In the absence of coupling, each oscillator would settle onto its limit cycle (circle) and rotate at its natural frequency. Starting from a random initial condition, the oscillators self-organize by adjusting their amplitudes and are pulled toward the mean field (asterisk) that they generate collectively; then, they sort their phases so that the fastest oscillators are in the lead. Ultimately, they all rotate as a synchronized pack, with locked amplitudes and phases. Reprinted, with permission, from Strogatz (2001).

connected together, they may produce a common intermediate global frequency. This is not a simply linear sum of the frequencies because in the functionally connected scheme each neuron fires phase-locked to the global rhythm. If one generator temporally exceeds the common tempo, the others absorb the excess, forcing it to slow down. Conversely, if it falls below the population rhythm, the other oscillators "pull" it back so that it catches up. The emergent population rhythm enslaves or supervenes the behavior of individual units (figure 4.9).

Coherence is the measure of the state in which two signals maintain a fixed phase relationship with each other or with a third signal that serves as a reference for each.[36] The phase differences are often used to infer the direction of the force, although in most cases such inference is not possible.

Phase-locking refers to the mutual interaction among oscillators by which the phase difference between any two oscillators is fixed. This measure is independent of the amplitude changes.[37] Phase-locking or phase-coupling can occur between oscillatory and nonoscillatory events as well, such as phase-locked

36. Coherence is a measure of phase covariance, which is quantified as the cross-spectrum of two signals divided by the product of the two autospectra. Because it measures spectral covariance, it cannot reliably separate amplitude and phase contributions. Phase-locking statistics can quantify phase coherence between two signals independent of the amplitudes of the respective signals (Lachaux et al., 1999).

37. For statistical methods of phase-locking, see Hurtado et al. (2004).

discharge of irregularly spiking neuron and an oscillator. Often, the term *entrainment* is used for such cases.

Cross-frequency phase synchrony can occur between two or more oscillators of different integer frequencies, when the oscillators are phase-locked at multiple cycles. If two oscillators differ in frequency and cannot fix their phases, they nevertheless can produce a transient and systematic interaction, called *phase precession* or *phase retardation.*

Phase reset of one or many coupled or independent oscillators can occur if a punctuate input forces to restart the oscillator(s) at the same phase. A related phenomenon but one involving different mechanisms, is *phase synchronization,* a stimulus-induced oscillation in two or more structures with transient coherent phase. *Phase modulation of power* occurs between a slower and faster rhythm, where the power of the faster oscillator varies as a function of phase of the slower oscillator.

Induced rhythms at two or multiple locations can be brought about with or without phase synchrony by a slowly changing input. Even if the oscillators are not coherent with each other, their power can be *comodulated.* This is sometimes referred to as *amplitude envelope correlation,* since the integrated envelopes of the signals are compared. It conveniently allows comparison of the amplitudes of any frequency band. Large-frequency mismatch or strong coupling can lead to *oscillation death* or *quenching.* This short list of terms is far from exhaustive but sufficient for the understanding of most of the oscillatory phenomena discussed in this volume.[38]

Naive wisdom would demand that one should use all methods described in this Cycle, in all possible combinations and in every experiment to get the best result. However, no serious mentor would provide such foolish advice to a student. The reason is that each of these techniques is very complex, and a thorough understanding of each requires several years of hard work and study. Furthermore, simultaneous application of multiple methods is often detrimental for various technical reasons. So when it comes to the important question of choosing the best method for understanding the brain, I pass along the advice I learned from my professor of pathology György Romhányi: "The best method for investigating any issue is your method." Choose one or two or three methods and learn all their pitfalls and virtues so you can interpret your data better than anyone else. There is no "best" method.

Briefly . . .

Because the brain is organized at multiple temporal and spatial levels, monitoring brain activity requires methods with appropriate resolutions. To date, only a handful of recording methods are available, and none of them has the ability to "see"

38. In addition, physics describes a variety of dynamical synchronization phenomena that may have relevance to neuronal networks, including splay-phase states, collective chaotic behavior, attractor crowding, clustering, frequency locking, dephasing, and bursting (Tass, 1999).

simultaneously small and large areas at the temporal resolution of neuronal activity.

Field potential analysis (EEG and MEG), imaging of energy production in brain structures (fMRI), optical recording methods, and single-cell recording techniques are the principal techniques in contemporary cognitive-behavioral neuroscience for the study of the intact brain. Unfortunately, even their combined, simultaneous application in behaving subjects falls short of the goal of explaining how a coalition of neuronal groups generates representations of the environments and creates appropriate responses in a changing environment. In the brain, specific behaviors emerge from the interaction of its constituents, neurons and neuronal pools. Studying these self-organized processes requires the simultaneously monitoring of the activity of large numbers of individual neurons in multiple brain areas. Development of large-scale recording from multiple single neurons with tetrodes or silicon probes is an attempt in this direction. However, these methods are invasive and cannot be used for the investigation of the healthy human brain. Many other methods, such as pharmacological manipulations, macroscopic and microscopic imaging, and molecular biological tools, can provide insights into the operations of the brain, but in the end all these indirect observations should be reconverted into the format of neuronal spike trains to understand the brain's control of behavior.

Cycle 5

A System of Rhythms: From Simple to Complex Dynamics

> Ts'ui Pen . . . did not think of time as absolute and uniform. He believed in an infinite series of times, in a dizzily growing, ever spreading network of diverging, converging and parallel times. This web of time—the strands of which approach one another, bifurcate, intersect, or ignore each other . . .—embraces every possibility.
>
> —Jorge Luis Borges, "The Garden of Forking Paths"

Neurons and connections of the brain support and limit its self-generated, spontaneous order even in the absence of sensory inputs or motor outputs. As described in Cycles 2 and 3, its structural organization supports a high complexity of wiring architecture. However, not all neurons and connections are used all the time. Quite the contrary, only a small fraction of the rich possibilities are chosen at any one moment. The dynamically changing functional or effective connectivity gives rise to short-lived oscillations that are perpetually created and destroyed by the brain's internal dynamics. The central tenet of this Cycle, which is echoed throughout the book, is that brain dynamics constantly shift from the complex to the predictable.[1] Neuronal ensemble activities shuttle back and forth between the interference-prone complexity and robust predictable oscillatory synchrony. As I explain in this Cycle, this switching behavior is the most efficient way for the brain to detect changes in the body and the surrounding physical world, while preserving its autonomous internal organization.

1. Karl Friston emphasized the importance of short-lived transients in his "labile brain" series (Friston, 2000). According to Friston, brain dynamics move from a stable incoherence through dynamic instability to complete entrainment. A similar idea is echoed by the chaotic organization of Walter Freeman's "wave packets" (Freeman and Rogers, 2002; Freeman et al., 2003) and the "neural moment" of transient synchrony of Hopfield and Brody (2001). It is not clear, though, how stable incoherence (high entropy) can be maintained in an interconnected system, e.g., the brain. As Sporns et al. (2000a, b, 2002) have pointed out, high-complexity and high-entropy conditions require very different architectures.

How Many Brain Oscillators?

Since the seminal discoveries of Hans Berger (Cycle 1), oscillations have been documented in the brains of numerous mammalian species, ranging from very slow oscillations with periods of minutes to very fast oscillations with frequencies reaching 600 hertz.[2] Somewhat surprisingly, a functionally meaningful taxonomy of brain rhythms has not emerged until recently. The first classification, introduced by the experts of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology in 1974, was driven by pragmatic clinical considerations.[3] Following Berger's tradition, the subsequently discovered frequency bands were labeled with Greek letters, and the borders between the different bands were evenly and arbitrarily drawn (delta, 0.5–4 hertz; theta, 4–8 hertz; alpha, 8–12 hertz; beta, 12–30 hertz; gamma, > 30 hertz), like the straight-line country borders between the African nations drawn by the colonialists. The frequency border classification was done out of necessity, since the mechanisms and independence of the various oscillatory patterns were largely unknown at that time. The frequency coverage of the classified bands was confined by the EEG recording technology. The widely used mechanical pen recorders limited the upper border of frequencies, whereas electrode polarization and movement artifacts prevented routine observations at low frequencies. Thus, frequency bands below 0.5 hertz were not included or given names. Although the international classification of brain frequency bands continues to be of practical importance, its major disadvantage is its self-limitation. Rhythms generated by the same physiological machinery at different ages or in different species often fall into different bands with different names. For example, the hippocampal theta oscillation was discovered in the anesthetized rabbit, and because of its frequency coverage (2–6 hertz), the name "theta" was given. However, in the drug-free rodent, hippocampal theta should be designated theta-alpha, according to the committee's recommendation, since it varies between 5 and 10 hertz.

A useful taxonomy of brain oscillations would require that the individual oscillatory classes represent physiological entities that are generated by distinct mechanisms. The same mechanism giving rise to different frequency bands in different species or the same frequency bands in different states (e.g., sleep/awake, anesthesia) of the same species ought to be referred to by the same name, even though the dynamics underlying the rhythms may be different. Unfortunately, the exact mechanisms of most brain oscillations are not known. As an alternative approach, Markku Penttonen, a postdoctoral fellow in my lab, and I speculated that there might be some definable relationship among the various brain oscillators.[4] Penttonen

2. The first comprehensive review on the subject is Katz and Cracco (1971).

3. See International Federation of Societies for Electroencephalography and Clinical Neurophysiology (1974) and Steriade et al. (1990a).

4. Komisaruk (1970) has already suggested that the different brain and body oscillators are coupled by some mechanisms, but he assumed an integer phase-locked relationship between them.

reasoned that, if we found a quantifiable relationship among the well-documented few, perhaps we could make some predictions about the less-known ones.[5]

We began by looking at the relationship among three hippocampal rhythms observed in the rat: theta (4–10 hertz) and gamma (30–80 hertz) rhythms and a fast oscillation (140–200 hertz).[6] These rhythms are independently generated, because we have already observed that gamma oscillations persist without theta and compete with the fast oscillation. Beginning with these three rhythms, we tried to interpolate and extrapolate other classes and relate them to each other. We found the best fit based on a natural logarithmic scale. Using the mean frequencies of our initially identified rhythms, the mean frequencies of other oscillation classes were estimated. The predicted frequencies corresponded to the traditional beta and delta bands as well as to less-known slow oscillations that we designated slow 1, slow 2, slow 3, and slow 4. By plotting the frequency bands in increasing order of frequency, a general principle emerged: discrete oscillation bands formed a geometric progression on a linear frequency scale and a linear progression on a natural logarithmic scale (figure 5.1, bottom).[7] This simple graph allowed us to make some fundamental statements about brain oscillators. First, all frequencies from 0.02 hertz to 600 hertz are continuously present, covering more than four orders of magnitude of temporal scale. Second, at least 10 postulated distinct mechanisms are required to cover the large frequency range. Third, because a single structure does not normally generate all oscillatory classes, structures must cooperate to cover all frequencies. Different mechanisms in different brain structures can give rise to the same oscillatory band, but there should be at least one distinct mechanism for each oscillation class. Fourth, and perhaps most important, there is a definable relationship among all brain oscillators: a geometrical progression of mean frequencies from band to band with a roughly constant ratio of *e,* 2.17—the base for the natural (Napierian) logarithm. Since *e* is an irrational number, the phase of coupled oscillators of the various bands will vary on each cycle forever, resulting in a nonrepeating, quasi-periodic or weakly chaotic pattern: this is the main characteristic of the EEG.

All of this raises important questions: why are there so many oscillators? Why can the brain not use a single, fixed-frequency clock for all of its functions? There are multiple answers to these questions. Behavior occurs in time, and precise tim-

5. Our strategy of taxonomic classification of brain rhythms followed the tactic used by Dmitri Mendeleev for his construction of the periodic chart of elements. In 1860, Mendeleev attended the First International Chemical Congress in Karlsruhe, Germany, where the leading chemists of the day gathered to sort out contradictory lists of atomic and molecular weights. They left for home with unfinished business. However, the 34-year-old Mendeleev left the meeting with a grand research project in his mind: find a meaningful system among the known elements. Playing a jigsaw puzzle with the elements for nine years did not yield results. Yet, one night in sleep, "I saw in a dream a table where all the elements fell into place as required," remembered Mendeleev (Strathern, 2000). His taxonomy provided organization to inorganic chemistry.

6. Buzsáki et al. (1992), Penttonen and Buzsáki (2003), and Buzsáki and Draguhn (2004).

7. The described system of oscillators is characteristic of the cerebral cortex only. Most other brain areas can support only limited types of oscillations.

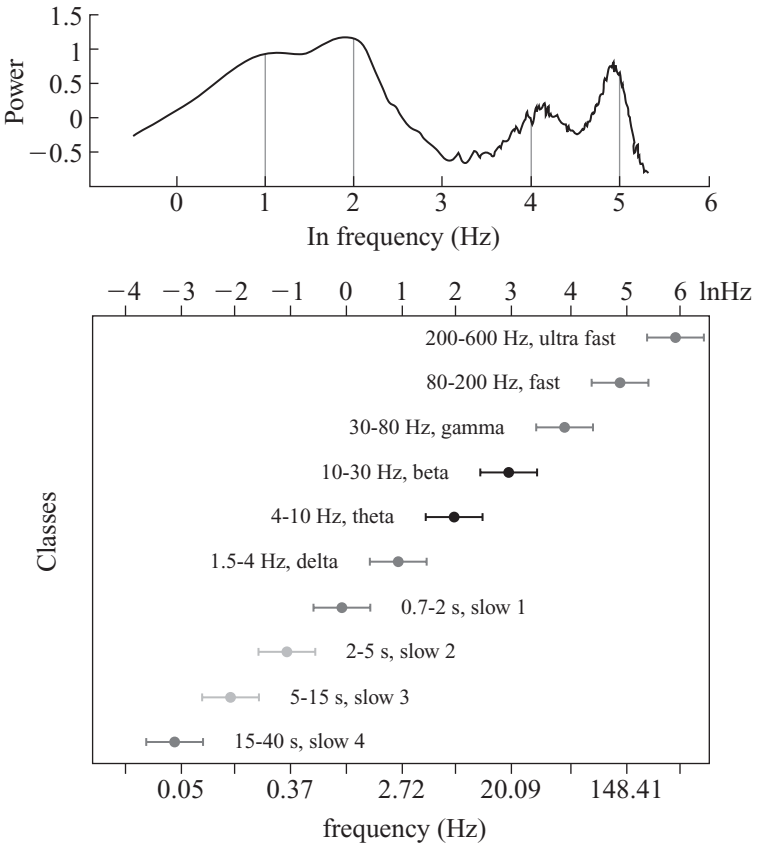

Figure 5.1. Multiple oscillators form a hierarchical system in the cerebral cortex. Top: Power spectrum of hippocampal EEG in the mouse recorded during sleep and waking periods. Note that the four peaks, corresponding to the traditional delta, theta, gamma, and fast ("ripple") bands, are multiples of natural log integer values. Bottom: Oscillatory classes in the cerebral cortex show a linear progression of the frequency classes on the log scale. In each class, the frequency ranges ("bandwidth") overlap with those of the neighboring classes so that frequency coverage is more than four orders of magnitude. The power spectrum was "whitened" by removing the log slope dominating the typical EEG spectrum (e.g., figure 5.2). Modified, with permission, from Penttonen and Buzsáki (2003).

ing from fractions of a second to several seconds is necessary for successful prediction of changes in the physical environment and for the coordination of muscles and sensory detectors in anticipation of environmental events. In principle, multiple tasks can be managed by a precise, single, fast clock and time division, as is seen in digital computers. Perhaps a de novo design of the mammalian brain would choose this solution. However, for sponges and other simple animals at early stages of evolution, fast responding was not a requisite for survival. All that is needed in these simple creatures is slow rhythmic movements for providing food

intake. Once a slow oscillator was invented, faster ones could be added as needed in subsequent evolutionary stages. New inventions of evolution are always built on the back of previously useful functions. Another argument for not using a single fast clock has to do with the wiring of the brain and the way neurons communicate with each other. Although action potentials, the digital means for communication between neurons, propagate in nerves innervating muscles relatively quickly (tens of meters per second), most axon collaterals in the brain are fairly slowly conducting (from centimeters up to a few meters per second). This sluggishness likely reflects an economical compromise of evolution between size and speed. Thicker axons conduct faster but occupy more space. But saving space comes with a price. For instance, informing multiple postsynaptic targets, located between 0.5 millimeter and 5 millimeters, of a single neuron may take 1 and 10 milliseconds, respectively; an order of magnitude time difference between the most proximal and most distant target! This problem becomes progressively larger when more complex events are represented in increasingly large neuronal ensembles. Oftentimes, the cooperative activities of hundreds of neurons are needed to discharge their postsynaptic target. The arrival times of action potentials from such a large number of sources must be coordinated in time to exert an impact. Recognizing somebody's face and recalling her first and last names, her profession, our last meeting, and our common friends are events that do not occur simultaneously but are protracted in time, since larger and larger neuronal loops must become engaged in the process. A number of psychological phenomena argue in favor of the idea that these cognitive events require hierarchical processing.[8] Separate processing requires the engagement of neuronal networks at multiple spatial scales.

Each oscillatory cycle is a temporal processing window, signaling the beginning and termination of the encoded or transferred messages, analogous to the beginning and end signals of the genetic code. In other words, the brain does not operate continuously but discontiguously, using temporal packages or quanta.[9] Designers of general-purpose programmable computers recognized a long time ago that networks with cycles have orders of larger capabilities than networks without cycles (e.g., a feed-forward net; see Cycle 9). The wave length of the oscillatory category determines the temporal windows of processing (figure 5.1) and, indirectly, the size of the neuronal pool involved. It follows from this speculation that different frequencies favor different types of connections and different levels of computation. In general, slow oscillators can involve many neurons in

8. A nice example is category learning (McClelland et al., 1995).

9. It was perhaps William James (1890) who first pointed to the segmentation of experience:

> The unit of composition of our perception of time is a duration, with a bow and a stern, as it were—a rearward- and a forward-looking end. It is only as parts of this duration-block that the relation of succession of one end to the other is perceived. We do not first feel one end and then feel the other after it, and from the perception of the succession infer an interval of time between, but we seem to feel the interval of time as a whole, with its two ends embedded in it. (p. 609)

James's observer is at an instant but embedded in the stretched time of the mind.

large brain areas, whereas the short time windows of fast oscillators facilitate local integration, largely because of the limitations of the axon conduction delays.[10]

Computation in the brain always means that information is moved from one place to another. Obviously, the path length of network connectivity is very critical in this process. Because the synaptic path length (recall the degree of neuron separation, as defined in Cycle 2) and effective connectivity determine the possible routes for shuttling information from structure to structure, the cycle lengths (i.e., periods) of the oscillation limit how far information gets transferred in one step. Fast oscillations, therefore, favor local decisions, whereas the involvement of distant neuronal groups in distinct structures in obtaining a global consensus requires more time.[11] This principle is nicely illustrated by a series of experiments by Astrid von Stein and Johannes Sarnthein at the University of Zurich. In their first experiment, they had human subjects view parallel grating stimuli with different numbers of bars per degree of visual field. Their main finding was that the power of the lower gamma-frequency band (24–32 hertz) increased with the number of bars per degree. Importantly, these changes were confined to the primary visual cortex. In the second experiment, everyday objects, familiar to all sensory modalities, were shown instead. Each object was presented as spoken word, written word, and picture. The modality-independent processing of inputs resulted in increased coherent activity between the adjacent temporal and parietal cortices. The main synchronization took place in the beta frequency range (13–18 hertz). A third set of experiments tested verbal and visuospatial working memory. This time synchrony was observed between the prefrontal and posterior associational cortices in the theta range (4–7 hertz). Although the extent of active neuronal assemblies could not be determined by this approach, the findings nevertheless support the idea that the size of the activated neuronal pool is inversely related to the frequency of synchronization.[12] The forthcoming Cycles discuss and attempt to justify these ideas in detail. For now, let us tentatively accept that the several oscillatory classes have distinct mechanisms, each serves a

10. The filtering property of the brain tissue is the standard explanation for the observation that the noise at a given frequency f is spatially correlated over a distance $L(f)$ that increases as f decreases (Voss and Clark, 1976). The physicist Paul Nuñez pioneered rigorous applications of physical wave propagation theories to brain waves (Nuñez, 1998). Physics provides a vast toolbox for treating wave phenomena mathematically. These techniques have provided some understanding of global brain phenomena in terms of the physical properties of its carrier medium. How far can we go with this physicist's view of the brain? While medium filtering is an important factor, it cannot explain the larger spatial extent of neuronal recruitment at lower frequencies or the behavior-dependent highly coherent gamma oscillations in distant brain areas (König et al., 1995; Varela et al., 2001; Buzsáki et al., 2004).

11. Benjamin Libet's brain stimulation experiments support this point. Libet's principal finding was that short trains of pulses evoked only unconscious functions, and the somatosensory cortex had to be stimulated for 200–500 milliseconds for evoking a conscious sensation of touch. To become aware of a sensory experience requires engagement of the appropriate brain networks for hundreds of milliseconds. The delay between Libet's "mind time" relative to physical time is a favorite argument of philosophers to question the unity of the mind and brain (Libet, 2004).

12. Von Stein et al. (1999) and Sarnthein et al. (1998).

different function, and each involves various magnitudes of neuronal pools. Because many of these oscillators are active simultaneously, we can conclude that the brain operates at multiple time scales.

Ultradian and Circadian Rhythms

The oscillators discussed so far are brain and neuron specific and emerge primarily through mechanisms that are unique to neurons. However, several other rhythms affect brain activity at a much slower pace, the most famous of which is the circadian rhythm with a 24-hour period.[13] As is the case with most oscillators, circadian periodicity can be maintained without an outside influence. The hypothalamic suprachiasmatic nucleus is usually referred to as the circadian "pacemaker" in mammals because it controls the daily fluctuations in body temperature, hormone secretion, heart rate, blood pressure, cell division, cell regeneration, and the sleep/wake periods. Unlike members of most network oscillators, each of the 20,000 neurons in the human suprachiasmatic nucleus is a circadian oscillator. This alone is not a unique feature of these neurons, since the molecular mechanisms that sustain the 24-hour rhythm are present in every cell of the body, although each cell in isolation would run a bit faster or slower than the 24-hour circadian cycle. The free-running periods of the individually isolated suprachiasmatic neurons in tissue culture vary from 20 to 28 hours, with firing patterns of some cells or groups with 6- to 12-hour phase shifts. In the intact brain, individual cells are entrained into coherent oscillation likely through their connectivity. As is the case in many other neuronal oscillators, the inhibitory neurotransmitter GABA and gap junction communication among the inhibitory neurons appear essential for the synchronization of individual neurons.[14]

What make the circadian clock so "slow" are the molecular mechanisms involved in its generation. It takes about 4–6 hours to make a protein from the gene. Internal timing is achieved through a complex feedback loop in which at least four freshly produced proteins participate. Two proteins, active in the morning, begin to produce a second set of molecules that accumulate during the day. In the evening, this second set of proteins inactivates the daylight-active proteins. The inactivation process involves genes in the nucleus. For example, in the fruit fly (*Drosophila*), a messenger RNA is transcribed from the period (*per*) gene, which in turn initiates the production of PER protein. The accumulating protein in the

13. From Latin *circa* (about) and *di* (day), meaning "about a day." Diurnal and nocturnal refer to patterns during the day and night, respectively, whereas ultradian rhythms are shorter periodic changes, also locked to the 24-hour cycle. The discipline of chronobiology is fully devoted to the study of body time, the impact of cyclic variations on health and disease ("chronotherapy").

14. Liu and Reppert (2000) have shown that synchronization of suprachiasmatic neurons is mediated mostly by GABA acting on $GABA_A$ receptors.

cytoplasm enters the nucleus and suppresses further messenger RNA production. The result is a reduction of PER with reduced suppression of the messenger RNA production, and the cycle can start again. The real picture is a lot more complex and involves interactions among the proteins themselves and multiple autoregulatory transcriptional/protein translational feedback loops.[15]

On the input side, timing of the circadian clock can be delayed or advanced by light, which in mammals is detected by the retina in the eye. In the retina, a small group of scattered ganglion cells contain the photoreceptor melanopsin and ambient light directly makes these neurons fire. The exclusive brain target of this special group of light-detecting neurons is the suprachiasmatic nucleus. Phase-locking of this "master" circadian clock leads to the production of hitherto unidentified molecules that work as output signals and synchronize the cycling of all individual cells in the body. In contrast to "simple" relaxation oscillators, several daily pulses may be required to bring the multiple partners of the circadian clock—including the sleep/wake cycle, body temperature, hormone secretion, and physical and mental functions—to a full reset and phase synchrony. All travelers are aware of this synchronization problem. "When you go [from America] to Europe, the soul takes about three days longer to get there," noted the writer-traveler Julio Cortazar.[16]

Embedded within the circadian cycle are at least two well-documented ultradian rhythms. The faster one recurs at approximately 90–100 minutes, whereas the mean duration of the slower one is 3–8 hours, with the shorter component superimposed upon the longer one.[17] Studies of the circadian and subcircadian rhythms form a new and fast-growing discipline that is gaining increased attention in medicine, psychiatry, and sleep research. What interests us most in the context of this Cycle is the relationship between these molecular oscillators and the faster neuronal rhythms. The observation that isolated single neurons of the suprachiasmatic nucleus vary their firing rates, emitting about twice as many spikes during the light phase as in the dark phase, proves the existence of a mechanism that translates molecular changes to spiking output. These output spikes can affect other neuronal oscillators in other parts of the brain. On the feedback side, suprachiasmatic neurons are affected not only by light but also by the global activity of the brain. For example, following sleep deprivation

15. The positive elements of this loop in the mouse are the transcription factors CLOCK and BMAL1, which drive three period genes (*mPer1–mPer3*) and one cryptochrome gene (*mCry1*). The mPER and mCRY proteins form heterodimers and negatively regulate their own transcription (Kume et al., 1999). Other key reports in this field include Konopka and Benzer (1971), Menaker et al. (1978), Pickard and Turek (1983), and Allada et al. (2001). The book by Foster and Kreitzman (2004) is an entertaining introduction to the daily cycles of life.

16. The quote is from a book (*Los Autonautas de la Cosmopista*) by the Argentine writer Julio Cortazar written together with his wife, Carol Dunlop, on a 33-day trip from Paris to Marseilles, as cited in Golombek and Yannielli (1996).

17. A useful collection on subcircadian rhythms in the body is in the volume edited by Hildebrandt (1957).

there is a rebound of prolonged sleep. In turn, such rebound sleep activity has a profound effect on the activity of suprachiasmatic neurons.[18] It is also significant that extension of the natural logarithmic relationship among neuronal oscillators extrapolates faithfully to the periods of ultradian and circadian rhythms.

In the past, brain oscillators were studied in isolation. Recently, we have begun to see them as part of a system of oscillators with an intricate relationship between the various rhythmic components. Considering the short path lengths of anatomical connectedness in the cerebral cortex, this complexity may not be surprising. Nevertheless, future systematic work is needed to decipher the general rules and mechanisms of coupling among the neuronal rhythms occupying multiple spatial and temporal scales.

The 1/*f* Statistical Behavior of EEG

One grand question about the brain is how the microscopic laws of cell discharges and synaptic activity can lead to a complex system organized at multiple time scales. The inverse relationship between oscillation classes and the magnitude of neuronal recruitment provides some interesting clues about the brain's long-time and large-scale behavior. When a goal is scored in a football stadium, the coordinated roar of fans can be heard for miles, in contrast to uncoordinated local conversations, which are lost in the background noise. Similarly, slow rhythms involve very large numbers of cells and can be "heard" over a long distance, whereas localized fast oscillations involving only a small fraction of neurons may be conveyed only to a few partners. The "loudness" feature of the various network oscillations can be quantified easily by Fourier analysis (Cycle 4). Once the signal is decomposed into sine waves, one can construct a power spectrum of the frequencies, a compressed representation of the relative dominance of the various frequencies. Although power spectrum ignores the temporal variation of the signal, it provides a quantitative assessment of the power relationship between the frequencies. In figure 5.2, the logarithm of the density is plotted against the logarithm of the EEG frequency. In this so-called log–log plot, we see a straight line, the hallmark of scale-free systems (i.e., systems that obey power laws; Cycle 2). By and large, the amplitude (square root of power), A, increases as the frequency, f, decreases, as expressed by the inverse relationship, $A \sim 1/f^{\alpha}$, where α is an exponent. The physicist's reaction to such a relationship is that the EEG reflects nothing special except the internal "noise" of the brain, generated by its active and passive components. At first glance, this conclusion seems diametrically

18. Deboer et al. (2003) found that changes in vigilance states are paralleled by strong changes in the spiking activity of suprachiasmatic neurons and concluded that the circadian clock can be substantially modified by afferent information from the brain.

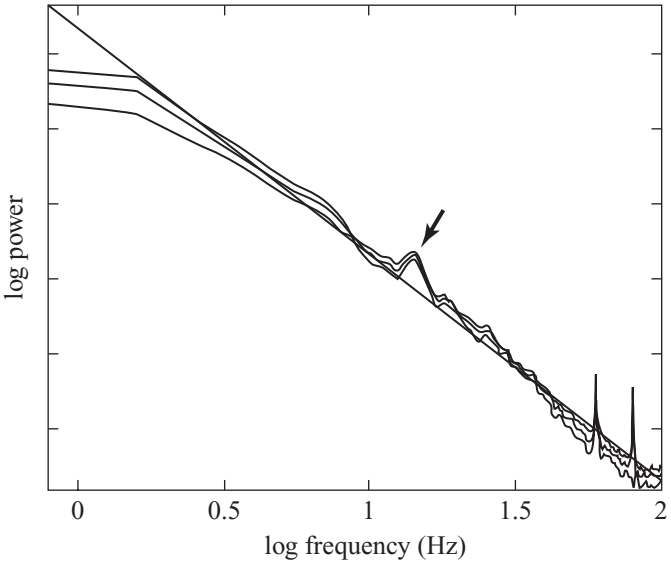

Figure 5.2. Power spectrum of EEG from the right temporal lobe region in a sleeping human subject (subdural recording). Note the near-linear decrease of log power with increasing log frequency from 0.5 to 100 hertz, the characteristic feature of "pink" or "complex" noise. The arrow indicates the peak at alpha (~11 hertz). Reprinted, with permission, from Freeman et al. (2000).

opposite to our suggestion above that the brain generates a large family of oscillations that allows for processing and predicting events at multiple time scales. Random noise does not allow any prediction. However, the noise with the "one over f" power spectrum is a special noise (also called "pink" noise).

A critical aspect of brain oscillators is that the mean frequencies of the neighboring oscillatory families are not integers of each other. Thus, adjacent bands cannot simply lock-step because a prerequisite for stable temporal locking is phase synchronization. Instead, the 2.17 ratio between adjacent oscillators can give rise only to transient or metastable dynamics, a state of perpetual fluctuation between unstable and transient phase synchrony, as long as the individual oscillators can maintain their independence and do not succumb to the duty cycle influence of a strong oscillator.[19] In the parlance of nonlinear dynamics, the oscillators are not locked together by a fixed point or attractor (phase), but they attract and repel each other according to a chaotic program and never settle to a stable attractor. A main reason for this recklessness is the presence of multiple oscillators that perpetually engage and disengage each other. Locally emerging stable oscillators in the cerebral cortex are constantly being pushed and pulled by the global dynamics. Nevertheless, despite the chaotic dynamics of the transient coupling of

19. For a didactic explanation of chaotic coupling of oscillator pairs and their ability to generate metastable saddle dynamics, see Bressler and Kelso (2001).

the oscillators at multiple spatial scales, a unified system with multiple time scales emerges. Indeed, the inverse relationship between frequency and its power is an indication that there is a temporal relationship between frequencies: perturbations of slow frequencies cause a cascade of energy dissipation at all frequency scales. One may speculate that these interference dynamics are the essence of the global temporal organization of the cortex.

In most illustrations, the log–log linear relationship breaks off below 2 hertz (figure 5.2). Does this mean that frequencies below 2 hertz follow a different rule? This departure from the $1/f$ line is partially due to the high-pass filtering feature of the routinely used amplifiers. However, if slow frequencies are also part of the scale freedom, they should have an impact on higher frequencies. Indeed, long-term scalp recordings confirm power-law scaling behavior for all frequencies tested and expand the temporal scale of the $1/f$ line beyond a minute.[20] This relationship indicates that amplitude fluctuation of, for example, an alpha wave at this instant in your occipital cortex can influence the amplitude of another alpha wave a thousand cycles later and all waves in between.

The scale-invariant feature of the EEG is the mathematical telltale sign of self-organization. The speed at which the power decreases from low to high frequencies measures the length of the correlations or, using another phrase, the "temporal memory effects" in the signal. This time memory effect is the main reason why the $1/f$ relationship is so intriguing. If there were no relationship among the frequency bands, the power density would be constant over a finite frequency range and the spectrum would be flat, $1/f^0$. Physicists call this pattern "white" noise. So there must be other colors of noise.

The third type of noise is "brown" noise. This time the term refers to the biologist Robert Brown, the discoverer of the cell nucleus, who also observed pollen particles performing a random dance in a water droplet: Brownian motion. In the case of brown noise, the power density decreases much faster with frequency ($1/f^2$) than is the case for pink noise. Brown noise is random at longer intervals, but it is easily predictable and strongly correlated at short intervals. For example, while touring a city without a guide or plan, we make turns at random at the intersections but our walk in straight streets is predictable ("random walk" pattern). Now, the interesting conclusion we can draw from this crash course on noise is that the $1/f$ behavior of EEG and magnetoencephalographogram (MEG) is the golden means between the disorder with high information content (white noise) and the predictability with low information content (brown noise).[21] The cerebral

20. The exponent of the $1/f^{\alpha}$ relationship varies somewhat across frequencies (Leopold et al., 2003; Stam and de Bruin, 2004) and behavioral conditions (eyes open vs. eyes closed) but is highly invariant across subjects (Linkenkaer-Hansen et al., 2001).

21. $1/f$ noise is ubiquitous in nature. In white noise, the power density is constant over a finite frequency range [$P(f)$ = constant power]. If we mix visible light with different frequencies at random, the resulting light is white, hence the name "white noise." It is also known as Johnson noise. If the different frequencies are mixed according to $1/f$ distribution, the resulting light is pinkish. In pink noise, the power density decreases 3 decibels per octave with increasing frequency (density proportional to $1/f$) over a finite frequency range that does not include direct current. Engineers use the terms "flicker" or

cortex with its most complex architecture generates the most complex noise known to physics. But why would the brain generate complex noise?

The brain-specific problem to be explained is why the power increases towards lower frequencies. The physicist-engineer explanation is that brain tissue acts as a capacitive filter so that the faster waves are attenuated more than are slow waves. This cannot be the whole story, however, because another main feature of the spectrum, namely, that perturbations of slow frequencies result in energy dissipation at all frequency scales, cannot be easily explained by discrete oscillators and passive filtering. Brain oscillators are not independent, however. In fact, the same elements, neurons, and neuronal pools are responsible for all rhythms. However, when the rhythm is fast, only small groups can follow the beat perfectly because of the limitations of axon conductance and synaptic delays. Slower oscillations, spanning numerous axon conduction delay periods, on the other hand, allow the recruitment of very large numbers of neurons. Thus, the slower the oscillation, the more neurons can participate; hence, the integrated mean field is larger. With local connections only, an emerging rhythm at one place would progressively invade neighboring territories, resulting in traveling waves.[22] At other times, the rhythm would emerge simultaneously at several locations and might be synchronized via the intermediate and long-range connections.[23] In short, the inevitable delays and the time-limited recruitment of neuronal pools can account for a good part of the $1/f$ magic.[24]

All of these EEG frequency relations would, of course, be of minimal interest even to oscillator aficionados if they were not intimately connected to behavior. If noise generation is simply a byproduct of brain operations, an inevitable inconvenience that has to be overcome, then we might sit back and simply marvel at the brain's extraordinary ability to compete with its self-generated noise. Alternatively, correlated noise production could be a deliberate "design" that must have important advantages and perceptual, behavioral consequences. From the latter viewpoint, the brain not only gives rise to large-scale, long-term patterns, but these self-organized collective patterns also govern the behavior of its constituent

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"excess noise." In brown noise, the power density decreases 6 decibels per octave with increasing frequency (density proportional to $1/f^2$) over a frequency range that does not include direct current. In brown noise, each point is displaced by a Gaussian (distributed) random amount from the previous point. This is also known as "random walk" noise (Mandelbrot, 1983). For an accessible introduction to the $1/f^{\alpha}$ and its more general form, the $1/x^{\alpha}$ behavior of various living and physical systems, see Gardner[a] (1978). For psychologists and behavioral scientists, I recommend the review by Gilden (2001).

22. Such a rare form of traveling wave is the so-called K-complex of light sleep (Massimini et al., 2004). For spiral waves and vortices, see Ermentrout and Kleinfeld (2001).

23. Studies using multiple extracellular and intracellular studies over a large portion of the cat neocortex by Steriade and colleagues provide ample evidence for the synchronous nature of slow (delta and slow 1) oscillations (Steriade et al., 1993b, d, e; see Steriade, 2001a, 2003).

24. For a detailed treatment of the physics of EEG, see Nuñez (1998).

neurons.[25] In other words, the firing patterns of single cells depend not only on their instantaneous external inputs but also on the history of their firing patterns and the state of the network into which they are embedded. Complex systems with 1/*f* behavior can be perturbed in predictable ways by various inputs. This susceptibility should apply to the brain, as well. Thus, it should not come as a surprise that power (loudness) fluctuations of brain-generated and perceived sounds, like music and speech, and numerous other time-related behaviors exhibit 1/*f* power spectra. Perhaps what makes music fundamentally different from (white) noise for the observer is that music has temporal patterns that are tuned to the brain's ability to detect them because it is another brain that generates these patterns. The long-time and large-scale note structure of Bach's First Brandenburg Concerto is quite similar to the latest hit played by a rock station or to Scott Joplin's Piano Rags.[26] On the other hand, both high temporal predictability, such as the sound of dripping water, and total lack of predictability, such as John Cage's stochastic "music" (essentially white noise) are quite annoying to most of us.[27]

If self-generated brain dynamics have a link to the spectral composition of speech and music, one might expect that the same dynamics would influence a plethora of other behaviors. Indeed, in addition to speech and music, the power law function is the best fit to the large data sets available on forgetting in humans and on other time-related behavioral patterns in a range of species, including habituation, rate sensitivity, and the many properties of time-based reinforcement effects and even synchronization errors of human coordination. Let us focus on some of them in more detail.

Weber's Psychophysical Law and Large-Scale Brain Dynamics

The anatomical-functional organization of the cerebral cortex should have consequences and limitations on cognitive behaviors as well. A well-known

25. The effects of the emergent, higher level properties on the lower level ones are often called "downward causation" or an emergent process (Thompson and Varela, 2001). Haken (1984) and Kelso (1995) refer to these features of dynamic systems by the term "circular causality." There is no identifiable agent responsible for the emergent organization; nevertheless, the pattern dynamics of the system can be mathematically described by the "order parameter," emergent property or "relational holism."

26. Voss and Clark (1975).

27. Interestingly, the complex predictability of sounds applies to monkeys, dogs, and other animals, as well, in which the pleasantness–annoyance dimension can be behaviorally measured. The psychologist Anthony Wright claims that rhesus monkeys hear music and other sounds in much the same way as humans do. His monkeys reliably identified the melodies of two songs, "Happy Birthday to You" and "Yankee Doodle Dandy," even when they were separated by as many as two octaves (Wright et al., 2000). For a review on "music perception" in animals, see Houser and McDermott (2003). Of course, the dynamics of cortical patterns in all mammals exhibit 1/*f* spectra.

psychophysical law that comes to mind in connection with the 1/*f* nature of cortical EEG is that of Weber and Fechner: the magnitude of a subjective sensation (a cognitive unit) increases proportionally to the logarithm of the stimulus intensity (a physical unit). For example, if a just-noticeable change in a visual sensation is produced by the addition of one candle to an original illumination of 100 candles, 10 candles will be required to detect a change in sensation when the original illumination is 1,000 candles.[28] According to Rodolfo Llinás at New York University, Weber's law also underlies the octave tonal structure of music perception and production. He goes even further by suggesting that *quale,*[29] the feeling character of sensation, may "derive from electrical architectures embedded in neuronal circuits capable of such logarithmic order." If so, then the 1/*f* dynamics may be the functional architecture underlying *qualia* and without the ability of a proper architecture to generate such temporal dynamics, no "feelings" can be generated (see Cycle 13 for a more extended discussion of this topic).

In the behavioral literature, interval or duration timing is often explained by a discrete pacemaker-accumulator mechanism that, similar to a stop watch, yields a linear scale for encoded time.[30] However, researchers have been aware of problems related to the intuitively simple ticking clock. The fundamental problem is that timing with a single clock implies similar accuracy at all time intervals; that is, the coefficient of variation (standard deviation divided by the mean) should not increase. Behavioral observations, however, show that the error of the hypothesized internal clock is proportional to the clock time; that is, they follow Weber's law or Stevens's power law, much like large-scale brain dynamics as measured by the EEG signal. Because the exponent of the power rule for interval magnitude and interval production errors is close to 1 (i.e., it is pink noise), some authors

28. Ernst Heinrich Weber noted that the increase of stimulus necessary to produce an increase of sensation in the various modalities is not a fixed quantity but depends on the proportion that the increase bears to the immediately preceding stimulus. The generalization of the relationship between physical stimuli and cognitive events has come to be known as psychophysics. Gustav Theodor Fechner, working at the same university (Leipzig) but unaware of Weber's work, described the same law but stated it in an equivalent mathematical form. When he learned that Weber had already discovered the relationship, he generously referred to his own observations as a consequence of Weber's law. Often, psychologists honor both by calling the relationship the Weber-Fechner law. Long before the Weber-Fechner law, the Pythagoreans recognized that human perceptions of differences in musical pitch correspond to ratios of vibrating string or air column lengths. It is believed that Pythagoras himself discovered that pleasing chords are achieved if length ratios correspond to successive elements of an arithmetic progression, 1/2, 2/3, and 3/4, which define, respectively, the octave, fifth, and fourth (see Curtis, 1978; Schwartz et al., 2003). Contemporary psychophysical research has refined and replaced Weber's law by a more precise Stevens's power law. Sensations (S) are related to the physical stimulus (P) as $S=P^n$, where n could be less than 1 but occasionally greater than 1 (Stevens, 1975).

29. In its broad "definition," *quale* is the qualitative content of experience, e.g., pleasure, pain, sorrow, and the feelings that emanate from perception of color, sound, etc. (Llinás, 2001; Tononi, 2004). According to the philosopher's definition, it is an attribute of something that we observe in our minds (e.g., Searle, 1992; Dennett, 1987).

30. Excellent books and papers deal with behavioral assessment of time in animals (Church and Gibbon, 1982; Killeen and Weiss, 1987; Staddon and Higa, 1999) and humans (Vierordt, 1868; Allan, 1979; Gibbon et al., 1984; Levin and Zakay, 1989; Tallal, 2004; Näätänen and Syssoeva, 2004).

argue that psychological time corresponds to real time, at least at the milliseconds to seconds scale. The psychophysical observations also indicate that there is not a certain point in this time continuum where timing is most accurate. In other words, time perception does not have a characteristic time scale; it is scale-free.[31] This may be because the brain, in contrast to computers and other single clock-dependent machines, uses a complex system of multiple oscillators for its operations with a power ($1/f$) relationship among them.

The progressively longer time required for recalling items from short-term memory after the initial fast recall of the first items may also reflect properties of systems with pink noise. An intuitive explanation of the storage-limiting effect in the brain is the time–space propagation of activity. Longer times allow propagation of activity to an ever-increasing population of neurons. However, information passing through spatially divergent neuronal networks is progressively more vulnerable to interference from other network effects (technically referred to as noise or "leakage"), therefore information deteriorates over time.[32] Evoked-potential experiments, recorded from the human scalp, nicely illustrate this conjecture. Sensory stimuli, such as flashes of light, evoke progressively longer latency, longer duration, lower amplitude, and more variable responses at successive stages of sensory pathways. Repeated presentation of such stimuli leads to modification (e.g., habituation) of the evoked responses. The most vulnerable components are the long-latency responses recorded from higher level associational areas, whereas the short-latency components, reflecting activity of early processing, are quite resistant to habituation.[33] The observations in humans echo earlier experiments in cats. When the source and intensity of the auditory conditioning signal were changed, the latency and amplitude of the early evoked

31. However, several investigators argue in favor of a characteristic "tempo" in both music (beat) and speech. Syllables are generated every 200–400 milliseconds during continuous speech in all languages.

32. Nieder and Miller (2003), examining the variability of single-unit activity from the monkey prefrontal cortex, concluded that encoding of numerical information follows Weber's law. They trained monkeys to discriminate between different numbers of dots. Control behavioral experiments showed that the monkeys indeed counted from 1 to 5. When plotted on a logarithmic scale, the tuning curves of "number neurons" could be fitted by a Gaussian with a fixed variance across the range of numbers tested. For "number neurons" in the parietal cortex, see Sawamura et al. (2002). The increasing magnitude of neuronal pool necessary for identifying higher numerosity can explain the scaling.

33. The earliest large scalp-recorded response is a negative potential (N1, 60–80 milliseconds after stimulus onset) followed by positive deflection (P1) at about 100 milliseconds. These "sensory" potentials are localized to the primary sensory cortical areas of the appropriate modality. The N2–P2 complex (around 200 milliseconds) is also known as mismatch negativity (Näätänen et al., 1987) because its amplitude is sensitive to the frequency mismatch of regular signals. Localization of the components is more difficult with scalp recordings, and they are collectively referred to as "cognitive" components. The most studied "cognitive" potential, so-called P300 (Sutton et al., 1965), is enhanced after an unexpected "oddball" event is embedded in a series of familiar events. A later, N450 (450 milliseconds) component is believed to reflect semantic encoding (Kutas and Hillyard, 1980). It is important to note that these evoked components reflect averaged waveforms of hundreds of repetitions. The single events can often be equally or better described as combinations of various oscillators. See Uusitalo et al. (1996) and Cycle 10.

responses faithfully reflected the parameters of the physical stimulus. However, the amplitude and shape of longer latency responses were essentially independent of the location and intensity of the signal source and were, instead, invariant concomitants of the significance of the signal, as verified by the overt behavior of the cats.[34] Overall, these observations suggest that successive stages of information processing have distinct and characteristic memory decays.[35]

The Fractal Nature of EEG

So far, we have tacitly assumed that the distribution of EEG and MEG power at different frequencies obeys the same rule, irrespective of the recording position in the brain or whether activity was monitored in a relatively small or very large neuronal pool. Indeed, this assumption appears to be the case, at least to a certain minimum spatial scale. Power spectra of long epochs of electrical fields, representing membrane voltage fluctuations of perhaps a few hundred neurons in the depth of the cortex when recorded by a microelectrode (micrometer range) or millions of neurons recorded by scalp electrodes (~ 10 centimeters), are essentially identical. Furthermore, the spectral content and frequency bands of the human EEG and the electrocorticogram of mice, rats, guinea pigs, rabbits, cats, dogs, and monkeys are remarkably similar. In other words, the long-term temporal structure of the macroscopic neuronal signal, reflecting the collective behavior of neurons that give rise to it, is macroscopically by and large similar in virtually all cortical structures and in brains of various mammalian species. This is a remarkable observation. In essence, the claim is that a collective pattern recorded from a small portion of the cortex looks like the pattern recorded from the whole.[36] This "scale invariance" or "self-similarity" is a decisive characteristic of fractals.[37] Fractal structures—such as river beds, snow flakes, fern leaves, tree arbors, and arteries—and fractal dynamic processes—such as pink noise, cloud formation, earthquakes, snow and sand avalanches, heart rhythms, and stock market price fluctuations—are self-similar in that any piece of the fractal design contains a miniature of the entire design. Regarding the collective behavior of neuronal

34. Grastyán et al. (1978).

35. Several recent experiments provide evidence for the scale-free and spatial fractal nature of scalp EEG recorded over extended durations (Freeman and Rogers, 2002; Freeman et al., 2003; Gong et al., 2003; Hwa and Ferree, 2002; Leopold et al., 2003; Le van Quyen, 2003; Linkenkaer-Hansen et al., 2001; Watters, 1998; Stam and de Bruin, 2004).

36. Even the power spectrum of synaptically isolated neurons, generating intrinsic (channel) noise, has a $1/f$ form (DeFelice, 1981; White et al., 2000).

37. The scale invariance of fractals implies that the knowledge of the properties of a model system at short time or length scales can be used to predict the behavior of the real system at large time and length scales. In our context, the EEG pattern recorded from a single site for a "representative" period of time can predict the EEG periods for very long times and at any other recording sites. Although neither of these statements holds true across all time and spatial scales, understanding the rules of space and time invariance of EEG is important.

signals as fractals with self-similar fluctuations on multiple time and geometry scales has potentially profound theoretical and practical implications for understanding brain physiology. It implies that the macroscopic EEG and MEG patterns describe the large-scale function of neuronal networks as a unified whole,[38] independent of the details of the dynamic processes governing the subunits that make up the whole.

The concept that physical systems, made up of a large number of interacting subunits, obey universal laws that are independent of the microscopic details is a relatively recent breakthrough in statistical physics. Neuroscience is in serious need of a similar systematic approach that can derive mesoscale laws at the level of neuronal systems.[39] The scale freedom of spatial and temporal dynamics in the cortex has emerged as a useful direction of research. Does this mean that some universal laws using a tiny bit of mathematics can help to bring the neuronal algorithms out into the light?

Pausing with this thought for a second, the math is not as simple as it looks. The seductively simple $1/f^{\alpha}$ function is, in fact, a very complex one. Every new computation forward takes into consideration the *entire past history* of the system. The response of a neuron depends on the immediate discharge history of the neuron and the long-term history of the connectivity of the network into which it is embedded. Assuming 100 independent neurons with spiking and nonspiking binary states, more than 10^{30} different spike combinations are possible. However, only a very small fraction of these combinations can be realized in the brain because neurons are interconnected; thus, they are not independent constituents. As a result, even a weak transient local perturbation can invade large parts of the network and have a long-lasting effect, whereas myriads of other inputs remain ignored. Although neuronal networks of the brain are in perpetual flux, due to their time-dependent state changes, the firing patterns of neurons are constrained by the past history of the network. Complex networks have memory.

Scale-Free Dynamics of Noise and Rhythms: From Complexity to Prediction

The novel spectral analysis methods and the mathematics of fractals and power laws have not only helped reveal the large-scale behavior of the brain signals but have also led to some fierce debate about the relationship between brain oscillations and noise. At the heart of the debate is the question of whether brain dynamics are characterized best by the various oscillators or "simply" pink noise.

38. Claims about the fractal nature of the brain are in fact quite old. The importance of localized vs. global or holistic brain operations is a long-standing controversy in philosophy, psychology, and neuroscience (Lashley, 1931). The presence of $1/f$ behavior indicates that the network dynamics are both local and global.

39. Kelso's book on the dynamical system properties of the brain (Kelso, 1995) is an important step in this direction.

The prominent alpha rhythms in human scalp recording notwithstanding, power spectra of long EEG segments, recorded over various behaviors, give rise to spectra without clear peaks. Rhythms come and go at various frequencies and various times, and their effect may average out in the long term. The feeling of permanence is only an illusion, and brain rhythms are no exception. Does this all mean that the recorded brain rhythms are simply extreme states of the neuronal noise generated by the busy brain works?[40] If EEG synchronization between different brain regions does not have a characteristic time scale, it is hard to understand how the effective connectivity of those regions can be modified according to rapidly changing behavioral needs.

The scale-free nature of global synchronization dynamics implies some specific predictions. One such explicit implication of the $1/f$ law is that, most times, brain dynamics are in a state of "self-organized criticality." This mathematically defined complex state is at the border between predictable periodic behavior and unpredictable chaos. In the context of brain dynamics, the implication of the concept of self-organized criticality is that the cerebral cortex displays perpetual state transitions, dynamics that favor reacting to inputs quickly and flexibly. This metastability is a clear advantage for the cerebral cortex since it can respond and reorganize its dynamics in response to the smallest and weakest perturbations. However, noise can be defined only in a finite temporal window, and the $1/f$ dynamics of brain activity are deduced from long temporal integration windows. Yet, at every instant, the state of the network is different; thus, the ability of cortical networks to respond to perturbation also changes from moment to moment.

A direct prediction of the self-organized criticality theory is that rare but extremely large events are inevitable, because at one point $1/f$ dynamics become supersensitive to either external perturbations or its internal processes, responding with very large synchronized events.[41] One may rightly mistrust this latter claim.

40. This issue has been debated for quite some time, and there are prominent people on both sides of the debate (e.g., Wright and Liley, 1996; Nuñez, 2000; Shadlen and Newsome, 1994, 1995). According to Erb and Aertsen (1992), "the question might not be how much the brain functions by virtue of oscillations, as most researchers working on cortical oscillations seem to assume, but rather how it manages in spite of them. (p. 202)."

41. The now classic mathematical thesis by Bak et al. (1987) combined two fashionable concepts—self-organization and critical behavior—to explain the even more difficult notion of complexity. This short paper's seductive claim is that, if a system has $1/f$ temporal scale and spatially fractal features, its behavior does not require any external "tuning" to undergo phase transitions (in contrast to e.g., water-ice phase transition that does require the external influence of temperature). Instead, complex systems spontaneously evolve to a state, where they lose their characteristic temporal and spatial scales, the result of which is that correlations run through the system at all scales. Self-organized criticality provides a definition of complexity: a system that exhibits $1/f$ and spatially fractal statistics. Complex systems with self-organized criticality include snow avalanches, earthquakes, forest fires, size of cities, airport traffic, Internet communication, blackouts in electric networks, size of companies, and biological mass extinctions. The attractive feature of the self-organized criticality hypothesis is that the statistical properties of these complex systems can be described by simple power laws. Several recent studies have suggested that EEG dynamics are characterized by self-organized criticality. See, e.g., Linkenkaer-Hansen et al. (2001), Freeman et al. (2003), Le van Quyen (2003), and Stam and de Bruin (2004).

In the lifetime of a normal brain, such unusually large events never occur, even though the ability of neuronal networks to generate such avalanches is illustrated by the supersynchronous activity of epileptic patients. The tensegrity dynamics of excitation and inhibition guard against such unexpected events. We have to recall that the EEG reflects the "average" behavior of neurons, with many interacting degrees of freedom. In the complex system of the brain, many degrees of freedom interact at many levels, such as neurons, mini- and macromodules, areas, and systems. Seemingly insignificant changes of the interactive constituents at any level can dramatically affect the course of events, as real-world tests of the self-organized criticality theory illustrate. For example, experiments with sand piles, rice piles, and other systems indicate that some minor changes of boundary conditions and space constants can often switch their critical dynamics to oscillatory behavior. For example, rice piles of certain types of rice grains display a broad distribution of avalanche sizes, thus supporting the theory. Sand piles, on the other hand, most often evolve into a temporal periodic state, presumably because gravity (a constant) can overcome the friction between sand grains.[42]

Another prediction of the postulated scale-invariant and spatial fractal feature of EEG is that knowledge of short-time information can be used to calculate long-range temporal correlations; similarly, knowledge about small-space scale information can estimate the global state. Neither prediction works perfectly well, as is demonstrated by numerous experiments in later Cycles. The rhythm versus the 1/*f* noise controversy should remind us of the somewhat banal, but nevertheless important, fact that general concepts such as power laws may be able to capture some aspect of a phenomenon without necessarily being able to explain all of its critical details. The 1/*f* feature of the EEG is obvious only when the events are integrated over a sufficiently long time and at a large enough spatial scale.

Why do some see convincing 1/*f* behavior, and others see mostly rhythms in EEG and MEG traces? Can the power spectrum be decomposed into individual rhythms generated by distinct neurophysiological mechanisms, or should we look for mechanisms that can generate pink noise without oscillations? Luckily, one can address the rhythm versus 1/*f* statistics controversy by removing the noise from the measured brain signal obtained during a particular behavior. This process is usually referred to as "whitening" or precoloring of the power spectrum by removing the correlated "pink" noise. The illustration shown in figure 5.1 (top) is an already whitened spectrum, which is why we can see clearly separable peaks at delta, theta, gamma, and fast ("ripple") frequencies. If there were no discrete, albeit interdependent, oscillations, the trace would be flat. Recall now that our logarithmic rendering of brain oscillators (figure 5.1, bottom) shows that in the frequency range where the 1/*f* relationship is continuous (2–200 hertz), five distinct oscillatory bands exist, each of which has a wide range of frequencies that fluctuate over time. The frequency, amplitude, and recurrence variability of the oscillators may account for the smoothness of the broad frequency range of the

42. Jensen (1998) is an excellent and entertaining short summary of the highlights and downsides of the self-organized criticality theory.

power spectrum constructed from long recordings without a need for generating extra noise.[43] Put bluntly, the brain does not generate complex noise directly. Instead, it generates a large family of oscillations whose spatial-temporal integration gives rise to the $1/f$ statistics. This is, in fact, the simplest way of producing complex noise. The bonus is that switching from complexity to the predictive oscillatory mode can be fast; such a transition is a major requirement for efficiently selecting a response from a background of uncertainty.

In the debate between pink noise and rhythms, we also have to remember how we generate the power spectrum and what we are trying to answer with it. Recall that the Fourier analysis works in the frequency domain and ignores temporal variations altogether. The power spectrum of Bach's First Brandenburg Concerto is the same, regardless of whether it is played forward, backward, or chopped into short segments and mixed so that even the best Bach scholars fail to recognize the masterpiece. Fast but critical transitions across patterns cannot be recognized in long-time power spectra. This, of course, applies to brain signals as well. All important serial effects, reflecting sequences of overt and covert behavior, are ignored by the summed power spectrum of the EEG and MEG. To compensate for such serious shortcomings, improved methods, such as the short-time Fourier transform or wavelet analysis, have been introduced. With these improved methods, sequential short epochs can be analyzed and the frequency structure displayed as a function of time.[44] This procedure is equivalent to calculating the power spectrum of the score in the First Brandenburg Concerto at every few hundred milliseconds. Obviously, there is still a lot of arbitrariness in the procedure, but it is a significant improvement over integrating the whole concert together over time. The most important advantage of such refined time series analysis is that now spectral characterization of EEG or MEG can be done in time windows that more faithfully correlate with behavioral changes. Using such refined brain–behavior analysis, spectra that correspond to identical behaviors can be combined and their frequency–power distributions can be contrasted across different behaviors. When the analysis is carried out in such a way, the presence of rhythms and their association with overt and cognitive behaviors often become obvious.[45] The simple reason is that transient behavioral changes and responses are often associated with characteristic but transient oscillations.

A similar contrast applies to the coherence of EEG activity as a function of distance. Long-term observations consistently show that coherence of neuronal activity rapidly decreases as a function of distance at high frequency but deceases less for low frequencies. On the other hand, short-lived but highly coherent oscillations in the gamma frequency band are often reported between distant sites processing different but related aspects of inputs (discussed in Cycle 10).

43. A somewhat similar idea is expressed by Szentágothai and Érdi (1989).

44. For the relationship between Fourier analysis and wavelet methods, see Cycle 4.

45. Stam and de Bruin (2004) also point out that investigators who do not report characteristic time scales in the EEG typically analyze long recording epochs with large variability. In contrast, studies that consistently report on distinct oscillations tend to sample short epochs of EEG signals.

These observations are important, because if the occurrence of a behavioral act is consistently associated with an induced rhythm in some structures, it likely bears physiological importance. In the critical state, the spatiotemporal correlations of neuronal interactions make the brain highly susceptible to perturbations, allowing for an instantaneous reorganization of effective connectivity.[46] Perturbations, such as sensory stimuli or motor output, could reduce the critical state and provide transient stability by oscillations. These transient stabilities of brain dynamics are useful to hold information for some time, as is the case while recognizing a face or dialing a seven-digit telephone number. Shifting the brain state from complex pink-noise dynamics to a state with a characteristic temporal scale is therefore an important mechanism that provides a transient autonomy to various levels of neuronal organization. I suggest that the ability to rapidly shift from the state of metastable pink noise to a highly predictable oscillatory state is the most important feature of cortical brain dynamics. In the high-complexity ($1/f$) regime of metastability, the brain is in a critical state capable of responding to weak and unpredictable environmental perturbations. By shifting its dynamics to an oscillatory regime, it instantaneously creates a state with linear variables, which is a fundamental physiological requirement for psychological constructs described by the terms "anticipation," "expectation," and "prediction."

Because most overt and covert behaviors are transient, their brain oscillation correlates are also expected to be short-lived. Thus, it would appear that averaging short-time power spectra is the perfect way to analyze brain–behavior relations. Indeed, stimulus-evoked averaging of brain potentials or metabolic changes in brain imaging experiments has been a standard procedure in cognitive and experimental psychology. The variability of the responses across trials is generally downplayed as unexplained variance or "noise" that needs to be averaged out to reveal the brain's true representation of invariant input. In functional magnetic resonance imaging (fMRI), the responses are often pooled and averaged across subjects to further reduce the variance. The real problem with the averaging procedure, of course, is that the state of the brain is constantly changing. State changes are hard to predict from behavior on a moment-to-moment basis. State variability is, to a large extent, internally coordinated. This "correlated brain noise," as it is often referred to, might be critically important because it is a potential source of mental operations.[47] The recorded signal, in fact, may contain more information about the observer's brain state than about the input, because the process is an "interpretation" or "construction" rather than a reflection, to use terms borrowed from psychology. In order to predict the present state of a brain, one needs to have access to its recent history.

46. Sensory, motor, and cognitive event-related "desynchronization" of the scalp EEG is just such a clear example of the perturbation of the postulated critical state of the brain. See discussion in Cycles 6 and 7.

47. For further arguments in favor of the importance of state variability in cognition and stimulus-induced effects, see Arieli et al. (1996), Friston (2000), Gilden (2001), and Buzsáki (2004).

The embodiment of recent history is the temporal correlation represented by the 1/*f* memory of scale-free systems. The term 1/*f* "memory" is a statistical statement and does not necessarily imply a direct connection with human recall or reminiscence. Nevertheless, because brain networks generate both behavior and electrical patterns, it is not unreasonable to suspect a link. Consider a simple syncopation or continuation experiment, in which subjects continue to reproduce a given temporal interval 1,000 times from memory after they are given 1-minute metronome training with the sample intervals. David Gilden at the University of Texas–Austin found that sequences of the errors can be best characterized with a 1/*f* power law. The translation of this statistical relation to behavior is that a given tapping error can affect the precision of the 100th future tap and on all taps in between. A remarkably similar temporal structure can be revealed by examining the long-term behavior of various brain oscillators. For example, alpha and gamma episodes come and go, but their occurrence is far from random. In fact, they have significant temporal correlations for at least a couple of hundred seconds and display a 1/*f* power spectrum with a striking resemblance to the behaviorally observed effects in both monkeys and humans.[48] The 1/*f* statistical signature is a potential link between brain dynamics and behavior. Ironically, this is the exact measure that we throw out with the current practice of averaging short-term data. This practice prevents us from addressing the important problem of response variability.

Noise and Spontaneous Brain Activity

The largest computer network of the neocortex yet built was constructed by Eugene Izhikevich and Gerald Edelman. Their three-dimensional model consisted of 100,000 neurons exhibiting some known cortical firing patterns. Each excitatory neuron was randomly connected to 75 local and 25 distant targets. Twenty percent of the neurons were GABAergic and wired locally, mimicking the proportions in the mammalian cortex. Despite such dense anatomical wiring, involving more than 7 million excitatory connections, neurons in the model remained dead silent unless external noise was provided to each neuron. At low levels of input noise, the system sustained oscillatory patterns with spatially uniform activity. High levels of input noise gave rise to asynchronous Poisson patterns of spiking activity that led to organized, sustained patterns.[49] Other computer networks do not fare better. In contrast to the brain, most current models of the brain or pieces of the brain do not give rise to true spontaneous patterns without some externally supplied noise. They either are dead silent or generate avalanches of activity in-

48. For 1/f noise in human behavior, see Gilden et al. (1995), Chen et al. (2001), Ding et al. (2002), Aks and Sprott (2003), for EEG measures, Linkenkaer-Hansen et al. (2001), Freeman et al. (2003), Leopold et al. (2003), Stam and de Bruin (2004).

49. Izhikevich et al. (2004).

volving nearly the whole population.[50] The usual explanation is that the network is not large and complex enough and therefore cannot generate enough noise. However, computer networks, including the supersized systems, fail to generate enough internal noise necessary for observing some desired patterns.

How large should a system be to generate continuous spontaneous patterns? My answer is that size is not the (only) issue.[51] Even a very small real brain or neuronal networks with just a few dozen neurons can solve complex problems that would make man-made computer-controlled robots jealous.[52] All real brains, small and large, possess spontaneous activity because they are complex enough. However, complexity does not simply emerge from increasing the number of constituents. Neuronal systems that consist of glutamatergic excitatory and GABAergic inhibitory neurons do not do much else than generate large epileptiform population discharges interrupted by silence. Indeed, this is exactly what an isolated piece of the mammalian cortex does. Fetal cortical tissue transplanted into the anterior chamber of the eye or into a blood-supplying cavity in the cortex generates synchronous discharges of various sizes followed by pauses of various lengths, a behavior not much different from that of sand piles. Isolated cortical slabs and cortical neurons grown as two-dimensional tissue culture generate similar burst/pause patterns. When isolated from their subcortical inputs, the nearly two million neurons in the rat hippocampus just sit and wait to be part of a giant collective scream.[53] These intermittent patterns are a far cry from the 1/*f* dynamics of the intact mammalian cortex.

Applying external noise to a network is convenient, but it has some inconvenient consequences. In Izhikevich's large model, noise intensity had to be increased fivefold to shift the system from avalanches to irregular patterns. At this high level of noise, synchrony occurred only in response to strong external inputs, and the average firing rate of neurons doubled. Most important, 10 percent of all action potentials occurred in response to the externally applied noise rather than to internally generated synaptic activity. This seems like an inefficient system

50. Some form of noise is included in all models to mimic the highly variable spontaneous spiking activity present in the intact brain (e.g., Usher et al., 1994). Some networks with sparse connectivity can generate irregular spike trains (van Vreeswijk and Sompolinsky, 1996; Amit and Brunel, 1997). However, these models are less sensitive to input perturbations and are quite unstable. Models of single oscillators, on the other hand, are too stable, and without some external noise, the spike patterns are very regular.

51. Voltage fluctuations in real neurons are limited by conductance increases (see Cycle 6) that accompany synaptic activity. Therefore, it seems unlikely that synaptic activity can generate large-enough white noise-like variability to sustain activity in model networks.

52. See e.g., Bullock and Horridge (1965) or Marder and Calabrese (1996) for spontaneous patterns in small neuronal networks.

53. For cortical transplants, see Bragin and Vinogradova (1983) and Buzsáki et al. (1989). The burst/pause patterns of cortical slabs resemble slow 1 oscillation (Timofeev et al., 2002) or epileptic discharges (Buzsáki et al., 1989). Traub and Wong (1982) provide a quantitative explanation for the avalanches in model networks. For the importance of subcortical neurotransmitters in preventing population bursts, see Steriade and Buzsáki (1990) and McCormick et al. (1993).

because such a large percentage of spikes are devoted to noise production. In models, this may not be such a big problem. However, energy calculations indicate that the brain cannot afford to waste so many spikes. Doubling the firing rate of neocortical neurons would exhaust their energy resources within minutes.[54] Furthermore, spikes generated by noise will propagate activity and interfere with signal-related computation. So, is noise just a waste or is there something good about it? Find out in Cycle 6.

Briefly . . .

The collective behavior of neurons, summed up crudely as the mean field (EEG and MEG) is a blend of rhythms. Neuronal networks in the mammalian cortex generate several distinct oscillatory bands, covering frequencies from < 0.05 hertz to > 500 hertz. These neuronal oscillators are linked to the much slower metabolic oscillators. The mean frequencies of the experimentally observed oscillator categories form a linear progression on a natural logarithmic scale with a constant ratio between neighboring frequencies, leading to the separation of frequency bands. Because the ratios of the mean frequencies of the neighboring cortical oscillators are not integers, adjacent bands cannot linearly phase-lock with each other. Instead, oscillators of different bands couple with shifting phases and give rise to a state of perpetual fluctuation between unstable and transient stable phase synchrony. This metastability is due to the presence of multiple coupled oscillators that perpetually engage and disengage each other. The resulting interference dynamics are a fundamental feature of the global temporal organization of the cerebral cortex. The power density of the EEG or local field potential is inversely proportional to frequency (f) in the mammalian cortex. This $1/f^{\alpha}$ power relationship implies that perturbations occurring at slow frequencies can cause a cascade of energy dissipation at higher frequencies, with the consequence that widespread slow oscillations modulate faster local events. The scale freedom, represented by the $1/f^{\alpha}$ statistics, is a signature of dynamic complexity, and its temporal correlations constrain the brain's perceptual and cognitive abilities. The $1/f^{\alpha}$ (pink) neuronal "noise" is a result of oscillatory interactions at several temporal and spatial scales. These properties of neuronal oscillators are the result of the physical architecture of neuronal networks and the limited speed of neuronal communication due to axon conduction and synaptic delays.

Brain evolution opted for a complex wiring pattern in the mammalian cortex. The resulting $1/f^{\alpha}$ temporal statistics of mean field are the hallmark of the most complex dynamics and imply an inherently labile, self-organized state. Although brain states are highly labile, neuronal avalanches are prevented by oscillatory dynamics. Most oscillations are transient but last long enough to provide stability

54. Laughlin and Sejnowski (2004).

for holding and comparing information at linear time scales. Scale-free dynamics generate complexity, whereas oscillations allow for temporal predictions. Order in the brain does not emerge from disorder. Instead, transient order emerges from halfway between order and disorder from the territory of complexity. The dynamics in the cerebral cortex constantly alternate between the most complex metastable state and the highly predictable oscillatory state: the dynamic state transitions of the brain are of the complexity-order types. When needed, neuronal networks can shift quickly from a highly complex state to act as predictive coherent units due to the deterministic nature of oscillatory order.

Cycle 6

Synchronization by Oscillation

> If the past is over, and the future has not yet come, all that exists is now; so how long does now last?
>
> —St. Augustine

What is and what is not an oscillator in the real world are not always easy to determine. To start the discussion, here is a rule of thumb for a true oscillator: if it is broken into pieces, it no longer oscillates. For example, a watch is a true oscillator system, a machine with a functional unity, in which cooperation of all its parts is necessary to keep track of time. Each part is designed for a particular function to assist other parts. Although several parts and functions contribute to the maintenance of clocking, only two of these are truly critical: mechanism for ticking time (time constant) and energy to maintain ticking. In a more general sense, rhythms arise whenever positive and negative forces balance each other. The positive force drives the system away from one state, while the negative force pushes it back. Unfortunately, my high school physics rule of thumb often fails when it comes to brain oscillators.

Indeed, identification of the minimum conditions necessary for the maintenance of neuronal oscillation can be a daunting task for various reasons. First, oscillating systems can be built in various ways. Systems assembled from the exact same building blocks can generate different dynamics and functions, depending on their precise internal and intersystem connections. Some architectural designs promote synchronization while others resist it. Second, the take-it-apart, put-it-back-together recipe does not work well in complex neuronal systems. Third, the behavior of most brain oscillators cannot be easily identified with the known types in physics. But we have to begin somewhere. Perhaps the best way

to start is to examine some well-known oscillators in the physical world and compare their behavior to neurons and neuronal groups. After reviewing some prototype oscillators of physics, I turn to oscillating single neurons and networks. I also discuss the importance of neuronal synchronization and its role in the formation of functional cell assemblies and conclude that synchronization by oscillation is the simplest and most economic mechanism to bring together discharging neurons in time so that they can exert a maximal impact on their targets.

What Is an Oscillator?

Biological oscillators belong to the broad class of *limit cycle* or weakly chaotic oscillators.[1] To picture the abstract mathematical construct of the limit cycle, think of a racing car on a circular track. If the speed of the car is relatively constant, it will pass in front of you periodically. The reciprocal value of the time period is the frequency of the car's circular motion. The exact path of the car will vary somewhat in each round, bypassing other cars at different parts of the track, but this path variability is limited by the physical barriers of the track. The car can occupy any part of the track but should avoid the barriers. Thus, the track surface can be conceived of as the attractor of the car's orbit. To generalize, the limit cycle is an attractor to which the trajectories of the oscillation are drawn after perturbations, provided the system has run for "enough" time. It is this feature that gives limit cycle oscillators their name. The most familiar form of oscillation is the harmonic motion of the pendulum. The electrical current supplied to your home by your local utility company is also a harmonic oscillator, with a periodic sinusoidal oscillation of its amplitude at 60 hertz (or 50 hertz, depending on where you live). Harmonic oscillators, like the pendulum clock, are reasonable beat keepers and good predictors.[2]

Of course, racing cars do not keep a constant speed. In fact, if we watch the race from a point that allows only a limited view, we cannot tell whether the periodic and regular return of our favorite car is achieved by a constant or variable speed. In theory, the car can idle for nearly the entire cycle period and finish the circle at a very high speed. Or it can just run slowly at the beginning of the circle

1. A weakly chaotic system is a system that is sensitive to the initial conditions (i.e., it is chaotic). For a thorough discussion of various oscillators, see Pikovsky et al. (2001). Strogatz's bestseller *Sync* (Strogatz, 2003) is an easy read. For biological oscillators, I recommend Winfree's classical book (Winfree, 1980) or Glass and Mackey (1988) The reviews by Kaplan and Glass (1995) and Glass (2001) are brief but comprehensive.

2. A harmonic oscillator is any physical system that varies above and below its mean value with a characteristic frequency, *f*. The playground swing is essentially a pendulum, a harmonic oscillator. You push when your velocity becomes zero at the top of swing to compensate for the lost energy, due to friction. The duration [*T,* (the reciprocal of frequency, $T = 1/f$), equal to $2\pi\ (l/g)^{1/2}$, where l = length and g = gravity], does not depend on the amplitude of the swing or your weight, only on the length of the swing.

and speed up for the remaining part. If the speed is not constant within a cycle, the oscillator is called nonharmonic. The output of nonharmonic oscillators can be virtually any shape. Because the output is generally characterized by a sudden change followed by a slow accumulation of energy, or relaxation, nonharmonic oscillators are often referred to as relaxation oscillators.[3] Biologists like to call them *pulsatile* oscillators. A household example of a relaxation oscillator is a dripping faucet. If the faucet is not turned off completely, it behaves like a metronome, generating water spheres and annoying sounds at regular intervals. The energy source that maintains the oscillation is the water pressure, whereas the balance between gravity and local viscosity determines the drop size. If the pressure is reduced, the interval between the drops increases; thus, the oscillator slows down, but the drop size remains the same. The frequency of the relaxation oscillator is calculated from the intervals between the pulses (water drops).

If the kitchen example seems too trivial, one can construct a similar mechanism from electronic components. Such an oscillator was first designed by Balthasar van der Pol in 1920 to model the perpetual contractions of the heart. The components of this simple electronic oscillator (figure 6.1) illustrate the principles and requirements that are sufficient to sustain oscillation. First, the oscillator has an energy source, in this case, a battery. Once the circuit is closed, the charges at the capacitor begin to accumulate. The speed of charge depends on the capacitance and resistance. The growth of voltage is analogous to the increase in the size of the water drop. When the voltage difference across the capacitance reaches a critical level, the gas in the neon tube becomes conductive and the tube glows for a short period of time. This energy-consuming process discharges the capacitance, and the neon tube becomes nonconductive again. This process is analogous to the drop of the water sphere. The interplay between two forces—the charge of the capacitance and discharge of the neon tube—can sustain the oscillation. Because of the slow charging and fast discharging features of the van der Pol relaxation generator, it is also called an "integrate-and-fire" oscillator. Modern versions of van der Pol oscillators are important circuits in radios, televisions,

3. Most biological oscillators are relaxation or pulsatile types, including heartbeats, respiration, walking, and hormone secretion. There are minimal requirements for an oscillator. The opposing forces of push and pull, positive and negative, excitation and inhibition combined with proper feedback are all that is needed (Wang, 2003). A relaxation oscillator is typified by a slow accrual and fast release of energy. Relaxation oscillators have only two free variables (voltage and voltage recovery). The standard form of a relaxation oscillator is $X=y-f(x)$, $Y=-ex$, where e is a parameter that modulates the rate of coupling between the slow and fast cycles of the oscillator. When e is close to 0, the oscillator spends most of its time in the slow accrual time scale, as is the case in a rhythmically discharging neuron at a low frequency with highly nonlinear behavior. Coupled relaxation oscillators in this slow mode synchronize with great stability. When e is close to 1, the variable y accrues very quickly, and the time spent in the fast release time scale becomes similar to the slow accrual time scale. In this case, the frequency of the relaxation oscillator is high, and the waveform is relatively sinusoidal (e.g., > 500 spikes/second for a neuron) and acts like a harmonic phase-pulling oscillator. Thus, it is possible to make a relaxation oscillator act like a sinusoidal phase-pulling oscillator by simply making it oscillate faster.

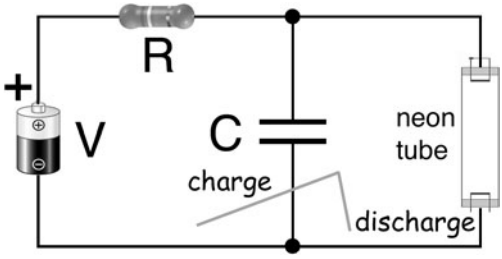

Figure 6.1. Principles of the relaxation (van der Pol) oscillator. The energy source (V) slowly charges the capacitance (C) through the resistor (R). When the voltage difference across the capacitance reaches a critical level, the gas in the neon tube becomes conductive (the tube glows) and discharges the capacitance. The interplay between two forces—the charge of the capacitance and discharge of the neon tube—can sustain perpetual oscillation.

and computers and are often used in modeling single neurons.[4] Harmonic and relaxation oscillators are the best understood types in physics. If we know the components of an oscillator, we can predict its dynamics. This bottom-up approach is often not very helpful in the brain because the components and their relationships are often too hard to decipher. Another approach is to determine the behavior of the oscillator and infer the underlying mechanism from the top down. This can be done because the general behavior of an oscillator and its response to perturbation depends on the type of the oscillator.

There are important differences between the behaviors of harmonic and relaxation oscillators (figure 6.2). In our racing car analogy, the frequency of the oscillation can be judged by measuring the speed (or phase angle) of the car at any short distance around the track, as long as the speed remains constant. In other words, the short-term and long-term behaviors of the harmonic oscillator are the same. Perturbing the oscillator is difficult, but it does not matter when (i.e., at what phase) the perturbation is exerted. If the car is moving at a constant speed and at a constant phase angle, an outside force (e.g., slight collision with another car) will have the same transient impact independent of the car's orbit on the track. The car twists and turns a few times and gets back to its limit cycle again. Similarly, if a pendulum clock is slightly perturbed, it exhibits a damped train of vibrations for a while before returning to its regular clocking rhythm. Harmonic

4. van der Pol (1889–1959) was among the first to recognize the importance of oscillations in biological systems. His pioneering work on hardware and mathematical modeling of heart contractions by coupled oscillators remains a masterpiece of biological physics (van der Pol and van der Mark, 1928). The slow accrual of energy needed to trigger an action potential (fast release of energy) in integrate-and-fire model neurons can be brought about by various time dynamics, providing rhythmic or stochastic firing or any pattern in between, depending on the properties of the network and the distribution of channels in the model neuron.

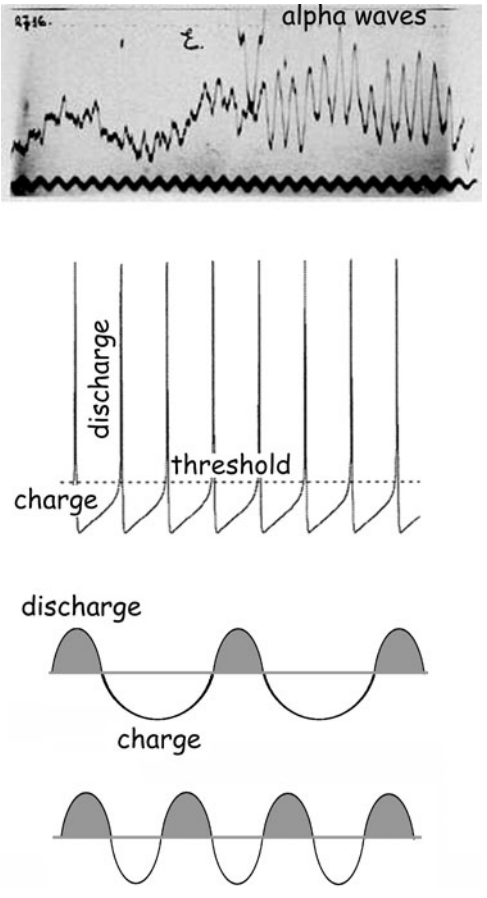

Figure 6.2. The alpha waves of Hans Berger share features with the harmonic (sinusoid) oscillator (top). Single-cell spiking oscillators are of the relaxation type, characterized by a slow accrual charge phase, threshold, and fast discharge (action potential) phase (middle). Increasing the frequency of oscillation can lead to equal charge (duty cycle; gray) and discharge periods, essentially a conversion of a relaxation oscillator into a harmonic oscillator (bottom).

oscillators, especially the variable frequency versions, are difficult to build and require a complicated multivariable coupling mechanism to keep the phase and frequency constant.

Relaxation oscillators display variable phase angles (velocity) in their orbits. Because of this nonlinear behavior, the estimation of the state of the oscillator (i.e., time or phase) between beats is not straightforward. There is no simple way to extrapolate the long-term frequency of water drops from observation periods shorter than the limit cycle.

Relaxation oscillators have three distinct states. The first is the excitable state

(energy accumulation phase; "ready to participate"), during which the oscillator can be perturbed. If one gently hits the faucet between the drops, the external force might produce a smaller sized drop, after which the process is reset to its full readiness state. The time between the perturbation and the next full-size drop is identical to the usual interdrop periods. Thus, in contrast to harmonic clocks, the relaxation oscillator wastes no time getting back to business as usual. The second state is called active (or duty cycle phase) and corresponds to the drop of water. Immediately after a drop, however, tapping at the faucet is no use, since water accumulation requires time. This early part of the accrual phase is usually referred to as the refractory period (third state). Since nearly all single neuron oscillators are of the relaxation type, these features should have a strong impact on the manner in which information is transmitted in neuronal networks.

The accrual and discharge phases can be referred to as receiving and transmitting modes, corresponding to the interspike and the spiking states of the neuron. For these reasons, a synchronously oscillating neuronal group can be perturbed by inputs only during the participating or ready state; they are immune to perturbations during the active state and the refractory period. Relaxation oscillators thus divide the labor between information transfer periods (duty or sending cycle) and readiness (or receiving) periods. Receiving and transmission of information are separated in time, and the magnitude of temporal separation is determined by the frequency and other details of the oscillating mechanisms. Mostly because of their phase reset properties, relaxation oscillators can couple together in large numbers. This capacity gives networks of relaxation oscillators the important ability to learn and store patterns. In summary, relaxation oscillations provide predictable windows of opportunities for neuronal assemblies to cooperate or, alternatively, ignore each other. This "gating" feature of oscillations has far-reaching consequences for the operations of neuronal networks.

Most often, periodic phenomena come in various disguises; it is not always easy to distinguish between harmonic and relaxation types or between true and spurious oscillators. This challenge is especially true for oscillating neuronal networks. Good time keepers, such as our circadian clock, work forever. During rapid eye movement (REM) sleep,[5] theta oscillation in the hippocampus is sustained for nearly the entire period of this sleep stage. These rhythms are therefore called sustained or autonomous oscillations that make use of a constant source of energy to counteract energy losses and are able to continue to oscillate virtually forever.

There are two extreme conditions under which oscillations can be generated. The simplest one is a phase-controlled energy source and a normally dampened system. A familiar example is the trick of getting yourself going on a swing by leaning back and forth with arms and legs timed (i.e., phase-locked) to the natural frequency of oscillation of the swing. The oscillation continues because you are periodically adding energy to keep the rhythm going. However, if the push is supplied by a friend and her pacing varies at her leisure, the swing becomes a forced

5. Sleep patterns are discussed in Cycle 7.

oscillator. In the second condition, the interaction occurs between the swing's features and a "noisy," or random, energy source without a clear event or source that is responsible for the oscillation period. Many intermediate forms between these extreme conditions exist, but the main principles are the same in all oscillators: a tension between *opposing forces* combined with a regenerative or *positive feedback.* In many cases, the temporal fluctuation of the energy and the degree of damping of the oscillatory system are not obvious, giving the impression of spontaneity even though the rhythm is supplied from an unrecognized outside source.

Thus far, we have considered oscillators in their steady state without getting into the thorny issue of how oscillations are brought about or die away. Most brain oscillators are not sustained for extensive time periods but rather come and go, for which reason they are called transient. Identification and quantitative description of transient oscillators can be very difficult. After all, what is an oscillator? If events occur at regular intervals millions of times, we have no problem. But what if they repeat merely 10 times, five times, or only once? Identification of the defining limit cycle is elusive with so few cycles. A pendulum without energy loss compensation is a damped or transient oscillator with a response that fades away over time. The waxing/waning oscillatory patterns that occur during the early stages of a night sleep, appropriately called sleep spindles, are prime examples of a transient neuronal oscillator. Because spindle events repeat many times during sleep, they can be lumped together for quantification. So, when it comes to a brief spindle of only two or three cycles, we generalize from the long-term observations and on the basis of waveforms and other features and accept or reject a pattern as a spindle.

Characterization of an oscillator is problematic not only when classified by a top-down approach but also when one attempts to define it with reverse engineering. An oscillator has numerous qualities, including rhythmicity, period, amplitude, duration of the duty cycle, entrainability, and robustness. Each of these features may be determined or influenced by several components of the oscillating system. One component may be responsible for the rhythm, another may adjust cycle duration, and yet another is critical for its amplitude. Without a full picture of all components and their interactions, it is often difficult to identify the necessary and sufficient elements of the oscillator and to delineate their specific contribution. The master–slave (i.e., pacemaker–follower) scheme is often difficult to justify, yet this relationship is frequently taken for granted in the neurophysiological literature. Occasionally, it is virtually impossible to draw a line between a true but transient oscillator and systems with properties prone to oscillate: resonators.

Resonance

If you happen to be standing near a piano with its top open and drop an object on the floor, you will see some of the piano strings begin to vibrate. This seemingly trivial phenomenon is called resonance, a condition in which energy is fed into a

system at the natural frequency of the system. In our example, the energy is sound, the system is the piano, and the resonant frequency corresponds the natural frequency of the responding strings.[6] A good piano has good resonance because it amplifies the sound. Oftentimes, resonance is unwelcome because it amplifies events we want to avoid. Engineers of bridges and skyscrapers constantly struggle with unwanted resonance. You might think that, with the advent of powerful computers, all possible conditions and potential dangers to such structures could be simulated and catastrophes prevented. Not quite. As recently as the summer of 2000, the Millennium Bridge, designed for pedestrian traffic between St. Paul's Cathedral and the Tate Modern Gallery in London, was closed only 3 days after its grand opening ceremony. Prior computer simulations and wind tunnel tests of the design had guaranteed that the bridge could withstand a 1 in 10,000-year return period for lateral wind forces. What was not tested or thought of in advance was how people walking across the bridge could introduce horizontal vibrations into the structure. Authorities closed the bridge immediately with the tentative diagnosis of resonance. It took more than a year and an additional £5 million to investigate and fix the problems. My real point is, however, that bridge failures happen not because of negligence but because oscillatory behavior in complex systems is not well understood.[7] If bridges are not complex enough, consider a neuron.

Oscillation and Resonance in Single Neurons

Before the 1980s, the main functions of a neuron were thought to be collecting information about its inputs (integrate), deciding how much information was enough (threshold), and sending this information, in the form of an action potential (fire), to its downstream peers.[8] Neurons and networks were believed to be silent unless excited by some outside sensory input. Intrinsic or spontaneous

6. Buildup of energy in the object forces it to resonate. If the energy dissipates, the resonance dampens. In the simplest case, a sudden energy pulse will start the oscillation, and its amplitude dampens quickly over time and stops. When an external force is supplied periodically at a frequency that matches the natural frequency of the object, it will begin to resonate. Adding the same forcing function at just the right phase during the oscillation makes the oscillation's amplitude grow larger and larger, unless energy loss or a negative force buffers it. Because driving forces at frequencies larger or smaller than the resonant frequency become less effective, resonators are also frequency filters. For the same reason, two or more oscillators at similar frequencies can resonate.

7. The Arup Group Ltd.'s website at http://www.arup.com/MillenniumBridge/index.html offers a detailed discussion about the challenges involved in building and securing this striking design. Another famous "bridge problem" was the collapse of the Tacoma Narrows Bridge in Washington State in 1940. In the numerous news articles that covered the event and in undergraduate textbooks, the collapse was presented as a real-world example of elementary forced resonance, but the real reasons are still debated (Billah and Scanlan, 1991).

8. The terms "upstream" and "downstream" imply that impulses travel in only one direction, as the flow of water. Given the multiple loops and high-dimensional organization of neuronal connections, these terms are often misleading. This is particular true in oscillating networks.

activity was described as a regular feature only in "primitive" neurons of invertebrates and in some "special" central pattern generators responsible for respiration, walking, and other rhythmic motor events. From this comfortable perspective, it appeared that studying the collective behavior of a large enough number of appropriately connected integrate-and-fire nodes ("neurons") would provide sufficient insight into the large-scale operations of the brain. In line with the program outlined by Turing (see Cycle 1), complexity was believed to be hiding in the special connectivity of uniform threshold detectors. That happy honeymoon of connectionist modeling came under fire in a milestone review in 1988, written by Rodolfo Llinás. The simple yet revolutionary message of his single-neuron manifesto was that neurons do a lot more than just passively integrate. The process that led to our current neuron concept was made possible by two critical innovations: the *in vitro* brain slice and the patch-clamp recording method, which allowed for a detailed and systematic examination of the biophysical features of neurons (see Cycle 4 for brief descriptions of these techniques).

The active neuron concept brought about a fundamental change in our thinking regarding the abilities of single neurons. The old view of the neuron as a bistable, well-behaving integrate-and-fire device was rapidly transformed. Today, we consider the neuron to be a dynamic piece of machinery with enormous computational power. The conceptual change can be attributed largely to the discovery of dozens of channels in the cell membrane, which allow differential movement of ions between the inside and outside of the cell. The open or closed state of these membrane channels is under the control of the membrane voltage, neurotransmitters and modulators, and other factors.[9] Voltage-gated channels are open only in a particular voltage range. In other words, the transmembrane

9. Channels are the structural units within the membrane that allow ion movement between extracellular and intracellular environments. The mechanism that regulates the probability and duration of the open state of the channel is referred to as "gating." Gating of ion channels operates through four different mechanisms: voltage gating, ligand gating, ion-dependent gating, and second-messenger gating. These four processes can cooperate dynamically. Membrane channels are more or less *ion selective,* i.e., preferably *permeable* to certain ionic species (K^+, Na^+, Cl^-, Ca^{2+}). When the permeability to a given ion increases, the membrane potential shifts to the *equilibrium potential* of this ion, where the tendency for net diffusion along the concentration gradient is exactly equal and opposite to the force exerted by the electrical gradient (the membrane potential). Hence, at the equilibrium potential, no net movements of that particular ion take place. However, most ion channels are not perfectly selective. Distinct channel types are characterized by their *reversal potential,* where none of the individual ion species is at equilibrium, but the total current carried by them sums up to zero. *Conductance* (the inverse of resistance) is a measure of how easily ions move across the membrane, and it depends on both the probability channel openings (i.e., permeability) and the concentration of permeable ions. The electrical *driving force* is the difference between the reversal potential and the prevailing membrane potential. Hence, the total ionic current (I) that flows across a population of channels at any given instant is obtained from a modification of Ohm's law, where $I = \text{conductance} \times \text{driving force}$. Important books on ion channels are Johnston and Wu (1994), Kaila and Ransom (1998), Koch (1999), and Hille (2001). For shorter reviews, see Kaila (1994) and Segev and Rall (1998).

voltage "gates" the channels' open/closed states. More precisely, the probability of their being open depends on the membrane potential, because channel opening and closing are probabilistic events.[10] The magnitude of ionic current that flows through a single channel is called conductance. If many Na^+ channels are open at the same time, the ionic driving force across the membrane is large; therefore, the depolarizing current is strong. We have already discussed two voltage-gated channels. These are the Na^+ influx and K^+ outflux-associated conductances responsible for the main part of the action potential (Cycle 4). The new knowledge supplied by the many biophysicists using the *in vitro* slice preparation is that there are many different voltage-gated channels, which are selective for a particular ion species and activated at various potential ranges with different kinetics. Other channels were shown to increase their open probability not by voltage but by various ligands, for example, neurotransmitters and drugs. Activation of yet another family of conductances depends on a critical concentration of other ions. For example, a particular class of K^+ channels is active only after a sufficient level of Ca^{2+} enters through the membrane. Importantly, these channels are distributed nonuniformly in the membrane. Some of them are present only in the soma, others in the dendrites with some regularity as a function of the distance from the soma. Prime examples include the transient K^+ channel (I_a) and the hyperpolarization-activated mixed cation current (I_h) (figure 6.3).[11]

So why are there so many channels? For one thing, different channel species have different temporal activation kinetics. Therefore, their complex dynamics, rather than a simple threshold, determine how eagerly and precisely the neuron responds to a given input. The newly found variety of voltage-, ligand-, ion-, and second-messenger-gated conductances endow neurons with intrinsic properties capable of generating a rich repertoire of activities, including oscillation and resonance at multiple frequencies. Single neurons respond with transient oscillations to a strong input. The natural frequency, or "eigenfrequency," of the damped oscillation is a result of two opposing effects. The passive leak conductance and capacitance of the neuronal membrane are mainly responsible for the low-pass

10. The power spectrum of "intrinsic" (i.e., non-synaptic) noise often takes the form of $1/f$ (Diba et al., 2004; for a review, see DeFelice, 1981). The computational analysis by Abbott and LeMasson (1993) nicely illustrates the consequences of dynamic regulation of conductances. The persistent Na^+ current (White et al., 1998b, 2000) and slow K^+ currents (Liebovitch and Tóth, 1991; Manwani and Koch, 1999) have been suggested to be the major sources of intrinsic noise. Importantly, these same channels are thought to be key players in subthreshold oscillations (Alonso and Llinás, 1989; Llinás, 1988).

11. For important physiological effects of I_a, see Hoffman et al. (1997). I_h channels have been studied extensively by Magee and colleagues (Magee, 2003; Magee et al., 1998). HCN1 channels, the molecular name for one type of I_h, increase fourfold from the soma to the distal dendrites (Lõrincz et al., 2002). For reviews on other channels, see Brown (1988), Storm (1990), and Vergara et al. (1998). Single-neuron models with detailed channel kinetics are described in Traub et al. (1994), Traub and Miles (1991), and Borg-Graham (1998).

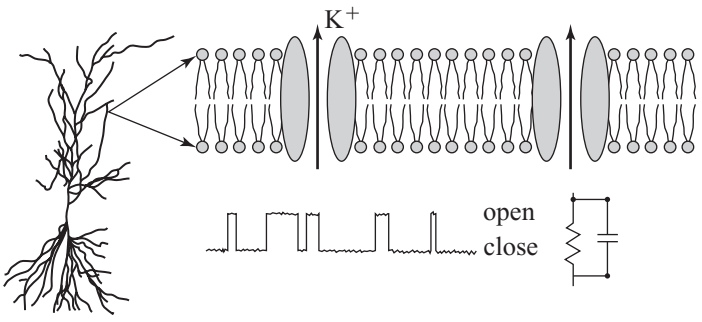

Figure 6.3. Pores or ion channels in the lipid membrane allow for the rapid and selective flow of inorganic ions (e.g., K^+ and Na^+) across cell membrane and are responsible for the generation of electrical signals inside and outside the neuron. Binding of neurotransmitters or the cell's membrane voltage controls the gating (opening and closing) properties of channels.

filtering property of neurons. As a result, responses of a passive neuron become progressively less reliable at higher frequencies. On the other hand, several voltage-gated currents, whose activation range is close to the resting membrane potential, act as high-pass filters, making the neuron more responsive and precise to faster trains of spikes. Neurons in which such conductances dominate are more efficient in transmitting fast inputs than slow inputs.[12]

The appropriate combination of high-pass (voltage-dependent) and low-pass (time-dependent) filtering properties of neurons can be exploited for the construction of biological resonators (band-pass filters), "notch" or band-stop filters, and subthreshold oscillators (figure 6.4). These resonant-oscillatory features allow neurons to select inputs based on their frequency characteristics. When embedded in an oscillatory or otherwise time-varying network, the time course and magnitude of the input predictably and continuously bias the open time probability of a multitude of ionic channels. If afferent activity is tuned to the preferred constellation of the neuron or part of it, the input will be amplified. If not appropriately tweaked, the neuron may elect to ignore the input altogether or respond with a considerable delay. The initiation and spread of the action potential are the result of a complex negotiation between afferent activation and the intrinsic features of the neuron. A neuron is a complicated resonator like a Stradivari violin, not necessarily tuned to a particular fundamental frequency, but endowed with a

12. Pike et al. (2000) demonstrate this general principle by comparing pyramidal cells and interneurons in the hippocampus. Pyramidal cells show a subthreshold resonance to inputs at theta frequencies (2–7 hertz) *in vitro,* whereas fast-spiking interneurons resonate at beta–gamma frequencies (10–50 hertz).

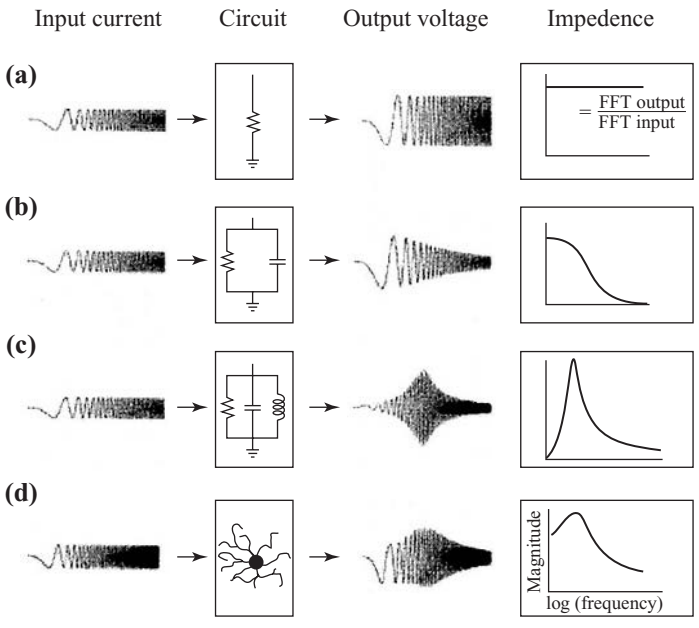

Figure 6.4. Resonant properties of neurons constrain them to respond most effectively to inputs at biologically important frequencies such as those associated with brain oscillations. Resonance is a property of the impedance (defined as frequency-dependent resistance). The frequency-dependent change of impedance can be determined by probing the circuit with an input current of varying frequency but constant amplitude (left column) and by observing the voltage response (third column). Passive neurons (with resistivity and capacitive features) act as low-pass filters. In contrast, active properties (e.g., voltage- and frequency-dependent synaptic currents) can act as high-pass filters. Most neurons, therefore, respond preferentially to inputs at a particular frequency. Reprinted, with permission, from Hutcheon and Yarom (2000).

rich response repertory over a wide range of frequencies.[13] Moreover, its response can be tuned by the large numbers of conductances that are differentially distributed in the somatodendritic membrane. Potassium channels are especially important in this process, because they counteract the input-induced depolarization and set limits on the overall excitability by controlling the interspike intervals. Potassium channels have the greatest diversity, with gating kinetics that spans several orders of magnitude. Importantly, they can be regulated by a variety of neuromodulators and cellular signals separately or in combination. For example,

13. In contrast to the neuron, the violin is a linear system, with the same Fourier components or "partials" appearing at the output of the violin as are generated by the sawtooth force of the bowed string. The amplitude of each partial in the radiated sound is determined largely by the mechanical resonances of the bridge and by the body of the instrument. Neurons, on the other hand, can dynamically change their resonant properties, as if the musician changed instruments between notes.

the amounts of neuromodulators released in the waking brain are much higher than in the sleeping brain, and activation of K^+ channels can increase spike timing reliability of cortical neurons at higher frequencies.[14] The ion composition of the various channels shows a large diversity among the various neuron types. As a result, cortical neuron classes have a wide range of preferred frequencies and spike timing properties, and their diverse frequency-tuning properties are important for setting network dynamics. For example, GABAergic interneurons respond with highest temporal precision to frequencies in the gamma band, whereas pyramidal cells respond more reliably to lower frequency rhythmic inputs.[15]

The astonishing conclusion from contemporary biophysics is that every part of the neuron can function as a resonator-oscillator. All the neuron needs is channel activity with opposing actions and feedback to sustain the ying-yang game. Thus, a single neuron consists of myriads of potential resonators whose properties differ due to the different channel properties and densities of the membrane along the somatodendritic and axonal surface. When a cell discharges at low and moderate frequencies, the distributed conductances are well coordinated, as expected from the large numbers of coupled relaxation oscillators. However, at high frequencies, the temporal choreography across the neuron becomes less perfect due to the inequalities of channel distribution in the different surface domains of the neuron. These simple biophysical considerations explain why the upper limit of the output of cortical pyramidal cells is a few hundred spikes per second, and why only much lower frequency spiking can be maintained in the distal dendritic arbors. Single-neuron behavior, therefore, is a direct consequence of the proper coordination of membrane channels along the somatodendritic domains of the neuron. The selective control of these channels by the network, in which neurons are embedded, is the reason behind my earlier claim that single neurons can perform in multiple ways.[16]

One can make the reasonable argument that oscillatory spiking in isolated leaky neurons has little to do with their routine behavior in the intact brain. Indeed, oscillatory spiking is easy to predict and therefore carries very little information. Furthermore, statistical characterization of spikes of individual cortical

14. D'Angelo et al.'s (2001) modeling experiments indicate that slow K^+ currents (I_{KS}) can affect the resonant properties of neurons and increase the reliability of spike timing at the preferred rhythmic input. The persistent sodium current (I_{NaP}) had the opposite effect. See also Hunter et al. (1998). In accordance with the computational modeling predictions, activation of slow K^+ conductances *in vivo* increased the temporal precision of spikes in the gamma frequency range (Penttonen et al., 1998). For an early example of neuronal resonance, see Knight (1972).

15. The reviews of Hutcheon and Yarom (2000) and Izhikevich et al. (2003) are excellent sources on neuronal resonance and filtering. For frequency differences in filtering ability by cortical pyramidal cells and different classes of inhibitory interneurons, see Markram et al. (2004), Gupta et al. (2000), Thomson (2000a,b), Pike et al. (2000), and Fellous et al. (2001). For theoretical background, see Abbott et al. (1997).

16. For an expanded argument for the same point, see Mainen and Sejnowski (1996) and Steriade (2004).

pyramidal cells in the intact brain does not give the impression of autorhythmicity. The apparent lack of rhythm at the single-cell level has been the source of some heated discussions about the role of oscillations and the nature of the neuronal code.[17] The issue can be formulated this way: is the default activity pattern of cortical pyramidal cells irregular discharge, or is the observed irregularity due to the property of the network they are embedded in? If the irregular firing pattern of neurons is due to their input control, then neurons in isolation should reveal their true nature. Richard Miles at the Pasteur Institute in Paris pharmacologically blocked the receptors responsible for excitation and inhibition in the hippocampus. Removal of excitation led to decreased excitability, whereas removal of inhibition enhanced activity, as expected. The surprise came when both types of receptors were blocked. Now neurons fired at a much higher rate and relatively rhythmically compared to the baseline *in vitro* conditions. Miles concluded that the default pattern of their recorded neurons was discharge, not silence.[18] The reason most neurons are silent (nondischarging) when they are part of the network is that physiological conditions provide a strong enough inhibition to change the default spiking activity of single cells into relative silence. The advantage of this arrangement is easy to see. If neurons were discharging at high rates all the time, the network would become noisy and neuronal impulse trafficking in large networks would be overwhelming and not particularly useful.

Ken Harris and Peter Barthó in my laboratory carried out a different but equally revealing experiment in the intact somatosensory cortex of the anesthetized rat. Our original goal was to separate the recorded cells into some rational groups on the basis of their firing patterns. There were two large groups, rhythmic and nonrhythmic. The striking observation was that the oscillation in individual neurons in the rhythmic group, pulsing at 7–13 hertz, went on independent of each other and of the local field, as if in an orchestra the players were not paying attention to either the other players or the conductor. We concluded that the anesthetic freed the neurons from their network obligations, and therefore, we could see their true individual behavior: oscillation.[19]

17. Numerous factors may be responsible for the apparent stochastic nature of single-unit discharge. The debate is reminiscent of the controversy between $1/f$ and the rhythmic nature of an EEG (Cycle 5). Investigators examining long-term firing patterns always find Poisson statistics in neuronal discharge activity (Bair et al., 1994; Koch, 1999; Shadlen and Newsome, 1994, 1995, 1998; Shadlen et al., 1996; Shadlen and Movshon, 1999), whereas researchers using short-term segments, induced by a certain behavior, often report on oscillations (König et al., 1995; Singer and Gray, 1995; Singer, 1999; Engel et al., 2001) or nonrhythmic but phase-locked discharge to field oscillations (Garcia-Sanchez, 1978; Csicsvari et al., 1999).

18. Cohen and Miles (2000).

19. Harris et al. (2003b). These experiments, however, tell us only that pyramidal cells can oscillate in isolation under the right circumstances. Under different conditions, they may fire only a few action potentials with decreasing frequency and stop discharging altogether. This accommodation of discharge frequency is due to several voltage- and ligand-dependent conductances that are activated by the spike-induced depolarization and Na^+ influx. However, once channels mediating these conductances are blocked, the neuron's spiking can become clocklike again (Penttonen et al., 1998).

Collective Neuronal Behavior Can Be Established through Synchrony

If you have seen Luis Bravo's Broadway extravaganza *Forever Tango,* you can picture the qualitative essence of neuronal synchrony: coupling through time by some invisible links. The essence of this sensuous dance that has enthralled both dancers and audiences for more than a century is the constant battle for control by either partner. However, there is no forcible action involved whatsoever. Instead, subtle facial expressions, harmonic body movement, light touch, and other invisible magic link the partners' swing in perfect unison.

Now we have a soft description of synchrony. However, providing a quantitative definition that satisfies physicists, engineers, and neuroscientists alike is a different matter altogether. In its broad definition, synchrony refers to the concurrence of events in time, a relation that exists when things occur simultaneously, such as two or many neurons firing within a short time interval. Events that occur at different times are asynchronous. Although this definition of synchrony is found in most textbooks, it is not particularly useful. For two observers to have expectations of something occurring "at the same time" is meaningful only if they see the same clock. Furthermore, a "discrete time window" should be defined for the judgment of simultaneity. Otherwise, it is impossible to name the time at which something occurs. If the same tune is played at the same time on the radio in both London and New York City, and the London broadcast is transmitted through the Internet, the tunes played by a radio and a computer in New York will not be judged as being simultaneous by a human listener. The same is true for an observer neuron that receives inputs from other neurons with different physical distances. If the difference in travel time of the action potentials from the presynaptic neurons is too long, the target neuron may treat them as asynchronous (separate) events.[20] In plain English, time alone cannot define the functional meaning of synchrony.

The judgment of simultaneity or synchrony of events is made by the observer, for example, a single neuron. Therefore, to be a useful concept in the brain, synchrony requires a discrete temporal window determined by a neuron or a neuronal pool. This period can be defined by the time within which some trace of an earlier event by one input is retained, which then alters the response to a subsequent event to other inputs. For a neuron, events that can be integrated over time (e.g., postsynaptic potentials) by some intrinsic mechanisms are therefore synchronous. The relevant temporal window for integration is the time within which a unitary

20. An experiment by Moutoussis and Zeki (1997) illuminates this point. If a stimulus is moving at 2 hertz, and the phase of movement and change of color occur simultaneously, it is very hard to tell *when* the color change occurs. A potential explanation of this observation is that processing of different features (motion and color) requires different brain circuits and different processing times. The subjects misbind the color and the direction of motion because color and motion are perceived separately and at different times, color being perceived first. In other words, the brain regards visual attributes as synchronous that are perceived together, rather than ones that occur together in real time.

postsynaptic potential, brought about by one input, decays back to baseline. Events that occur beyond this window are deemed nonsynchronous, because the earlier event does not have any impact on the later response. The term that most often refers to this decay is the membrane time constant of the neuron, which corresponds to tens of milliseconds in passive cortical pyramidal neurons.[21] So if synaptic inputs arrive no more than a few tens of milliseconds apart, they are synchronous from the neuron's point of view.

For real neurons, however, the integration time window is much harder to determine and depends on a variety of factors, such as replenishment of the neurotransmitter in the presynaptic terminal, the actual resistance of the membrane, receptor types, the immediate spiking history of the neuron, and the state of the various conductances in general. When the neuron is very active, it becomes leaky and can integrate over a much shorter window than at times of low activity. Other intrinsic mechanisms can expand the temporal span of integration. In other words, the time window of synchrony from the neuron's point of view varies over a wide temporal range and can be much shorter or longer than the membrane time constant of a passive neuron. As a result, a "single neuron moment" within which the neuron can integrate afferent activity is only tens to hundreds of milliseconds, not long enough to be useful for holding even a telephone number.

The effective integration window for synchrony can be much longer than the membrane time constant when it applies to a group of interactive neurons. For a group of neurons, the window size is typically determined by the readiness period of the ongoing population oscillation. The duration of the readiness state of the network oscillator, now at the neuron group level, determines the window of synchronization, which can be much wider than the properties of its constituent neurons would predict. The slower the rhythm, the wider is the window of opportunity for synchronization. In a wider time window, more neurons can be recruited from larger brain areas because synaptic and axonal conductance delays are less limiting; thus, the spatial extent of synchrony is much larger in the case of a slow rhythm.

The time window of synchronizing effects depends on the nature and details of the oscillator. For a harmonic oscillator, synchronizing forces should arrive in less then half the cycle period of the oscillator; otherwise, different subsets will fire out of phase and the network oscillation dies. For example, in the gamma

21. Time constant is the time at which the change in potential ΔV decays to $1/e$ (~ 37 percent) of its peak value. The time constant varies as a function of input resistance (increases with increasing membrane resistance because the electrical charge dissipates slower when the membrane is less leaky) and membrane capacitance (increases with increasing membrane capacitance because the electrical charge dissipates slower if the membrane has a higher charge storage capacity). The time constant for a passive cortical neuron is 10–50 milliseconds (Hille, 2001; Johnston and Wu, 1994; Koch, 1999). However, this figure refers to an inactive neuron with very high input resistance. Neurons in the intact brain are under constant bombardment from other neurons. These inputs activate channels, make the neuron leaky, and can reduce the neuron's input resistance several-fold (Kamondi et al., 1998; Borg-Graham et al., 1998; Paré et al., 1998; Destexhe et al., 2003). Importantly, in the waking animal, input resistance can be strongly affected by subcortical neurotransmitters, affecting mainly K^+ channels (Steriade and Timofeev, 2003). Synchrony from the neuron's point of view, therefore, fluctuates as a function of network activity.

frequency range (e.g., 50 hertz), excitatory inputs to all members should arrive within 10 milliseconds (half the period) to enhance the oscillation. Interestingly, this time window may be wider for coupling of relaxation oscillations. Because relaxation oscillations have unequal integration and output phases, the critical time windows vary depending on the nature of forces. For example, if in our gamma oscillator example the ratio between the accrual and duty-cycle phases is 4 to 1, inhibitory effects that tend to prevent early discharge have a time window of 16 milliseconds, whereas excitatory effects leading to neuronal discharges should arrive within only 4 milliseconds to maintain steady oscillation. The wider effective window for inhibition explains why inhibitory interneurons are so critical in clocking functions of the brain (Cycle 3). In summary, synchrony in neuronal networks can vary from milliseconds to seconds or even longer, depending on the period and exact architecture of network oscillations. The slower the oscillation, the less it depends on fast conducting long-range connections.

Synchronization is one of nature's most persuasive drives, extending from atoms to neurons, from the stock market to hurricanes. Synchrony occurs when some forces bring the events together in a given temporal window, determined by some systematic time constant built into the system. The real "cause" of synchrony is not always obvious. Some events, such as excitation, actively facilitate temporal cohesion. Alternatively, some events, such as refractoriness or inhibition, actively prevent the occurrence of an output and thereby regulate the probability of occurrence of the duty cycle. Excitatory feedback in recurrent neuronal networks is an especially effective method of recruiting large numbers of neurons within a short time period. A main physiological advantage of synchrony is that it brings about a rapid and large rise of population firing rate. [22]

Although stimulus-induced synchronization is often associated with increased firing rates of the responding neurons, ensemble synchrony can occur also in the absence of firing rate changes in individual neurons. In the latter case, increased synchrony is not possible to identify with standard single-unit methods because spikes of a single neuron do not inform us about cooperative performance. For example, during rest and slow-wave sleep, the firing patterns of individual hippocampal pyramidal neurons are characterized more or less by Poisson statistics. However, looking at a larger population can reveal an alternative perspective. Observing the neuron population as a whole, irregularly occurring, strongly synchronized ensemble patterns become obvious. From time to time, in 80- to 150-millisecond time windows, up to 18 percent of the pyramidal cells discharge a spike or a complex-spike burst, representing the most synchronous physiological

22. Karl Friston (2000) suggests that synchrony is just one possibility of neuronal communication. On theoretical grounds, he speculates that asynchronous coding provides rich, context-sensitive interactions. Indeed, if you know the transformation code between "ti-ti-ti, ta-ta-ta, ti-ti-ti" and S.O.S. and what the abbreviation stands for (Save Our Souls, the cry sent repeatedly by the radio operator of the *Titanic*), there is no need for synchrony. Although similar sequential activation of neuronal groups is surely a routine operation in the brain, it is not clear how a single neuron can be efficiently discharged by asynchronous activity of its upstream peers.

discharge pattern of the mammalian cortex. Obviously, such powerful population synchrony should have a profound influence on the downstream targets of the cooperating neurons, and without synchrony, no such effect is expected because individual neurons do not change their pattern or rate noticeably.[23]

Several fundamental points can be deduced from these observations. First, a population of neurons can have an explicit temporal dimension not present in the dynamics of single cells. Second, population synchrony, and hence enhanced output, can emerge even without modulation of the firing rates of individual neurons. Third, mean field activity, representing the spatial-temporal statistical properties of the nearby neuronal population, can serve as a useful reference to which activity of single neurons can be related. Some of these same points were discussed by Eilon Vaadia and colleagues at the Hebrew University in Jerusalem.[24] They recorded from pairs of neurons in the monkey neocortex in response to a meaningful stimulus and observed that the degree of the neurons' coherent firing changed in response to behaviorally relevant events, even though the firing rates of the neurons did not necessarily alter. Unfortunately, no local field potential was recorded in these experiments, so it remains to be revealed whether coherent changes at the population level were reflected by the mean field statistics. The most important message of these empirical observations in various cortical structures and species is that the information about the input can be embedded in the dynamic change of temporal synchrony even without an alteration of discharge frequency. And if no extra spikes are required to transfer information, no extra energy is needed.[25]

External and Internal Sources of Synchrony

A synchronizing influence can be an outside force or can emerge from within a self-organized system. Most often, these distinct influences cooperate, and it is difficult to distinguish their true origin. A useful example is the conductor's control over the members of an orchestra. If the cellists, first violinists, and other

23. The emergence of this self-generated synchrony in the hippocampus takes the form of a fast (140–200 hertz; "ripple") transient oscillation in the pyramidal cell layer of the CA1 region (Buzsáki et al., 1983, 1992; Buzsáki, 1989; O'Keefe 1976; Ylinen et al., 1995a; Csicsvari et al., 1998, 1999, 2000; for ripples in humans, see Bragin et al., 1999). Subsequently, we identified an analogous but even faster transient ripple synchronization in the somatosensory cortex of the rat (Kandel and Buzsáki, 1997; see also Jones and Barth, 1999; Grenier et al., 2001). Such fast patterns have been also reported from scalp recordings in humans (Curio et al., 1994), but their physiological or artifactual nature could not be established until they were observed in animal experiments. Fast (600 per second) oscillations have also been documented by magnetoencephalography in the piglet's somatosensory cortex in response to stimulation of the snout (Ikeda et al., 2002). The authors suggest that at least part of the oscillation is due to synchronous spiking in the thalamocortical terminals.

24. Vaadia et al. (1995).

25. An important practical implication of the information transfer by synchrony is that such important changes may remain undetected by fMRI.

players are randomly placed in the concert hall, and if the musicians' ability to listen to others is attenuated by placing wax in their ears, the conductor-mediated orchestration would still be apparent. Conversely, the piece can also be played without the conductor, based exclusively on intraensemble interactions. Similarly, the precise timing of central neurons depends not only on the physical inputs but also on the exchange of signals among central neuronal ensembles. These two sources of synchronization, externally driven and self-generated, should be distinguished because their tuning roles are often very different.[26]

External influence can be readily detected in early sensory pathways but can also be recognized even at higher order cortical centers. A particularly nice example of temporal patterning in the mid-temporal cortex of the monkey was provided by Tom Albright and his colleagues at the Salk Institute. They compared the effects of either constant-velocity or time-varying visual stimuli on neuronal responses. The responses to both stimulus configurations were characterized as rate-modulated Poisson spikes. Surprisingly, the speed at which the time-varying stimuli moved was reflected by the temporal precision of neuronal spikes within 3 milliseconds, on average. In this and other examples,[27] temporal coordination of ensemble synchrony is brought about by inputs from the physical world, much like the conductor's influence on the members of a symphony. Stimulus-related temporal coordination can be revealed by repeating the same physical signal and observing common features of the response. Since the early days of sensory neurophysiology, it has been known that neuronal responses vary considerably from trial to trial. This variability has been traditionally thought of as "noise" that should be averaged out to reveal the brain's true attitude toward the input.[28] However, the source of noise has never been identified and has been assumed to result from the brain's imperfections.

26. In experimental practice, disentangling stimulus-induced synchronization from network-induced synchronization is not simple because the percentage of coincident spikes increases as the square of the combined firing rate of neurons, even if they fire completely randomly. Induced rhythms usually do not have a time-locked relationship to the input (see Cycle 9).

27. Information-theoretic analysis revealed that the responses encoded only approximately 1 bit per second about constant-velocity stimuli but up to 29 bits per second about the time-varying stimuli (Buracas et al., 1998). Similarly, Ruyter van Steveninck et al. (1997) showed that the motion-sensitive neurons in the fly's visual system responded with irregular firing patterns to constant-velocity motion. However, more natural, moving signals yielded more reproducible spiking, in terms both of timing and of counting precision. They also found that temporal information about the spikes carried twice the amount of information as an equivalent (Poisson) rate code. These *in vivo* findings are reminiscent of the precisely repeating firing patterns of cortical pyramidal cells in response to intrasomatic injection of noisy depolarization (Mainen and Sejnowski, 1995). An explanation for these highly reliable repeating patterns is that the threshold of the action potential depends on the trajectory of the preceding postsynaptic potential and the immediate spiking history of the neuron (Azouz and Gray, 1999; Henze and Buzsáki, 2001). For behaviorally relevant examples of temporal patterning in central structures, see also deCharms and Merzenich (1996).

28. Analyses of spike trains in response to the same physical signal show that the coefficient of variation is usually close to 1, a telltale sign of an underlying Poisson process (Softky and Koch, 1993; Bair et al., 1994; Shadlen and Newsome, 1998; Stevens and Zador, 1998; but see Fenton and Muller, 1998; Csicsvari et al., 1999).

There are only two sources that control the firing patterns of a neuron at any time: an input from outside the brain and self-organized activity. These two sources of synchronization forces often compete with each other (Cycle 9). If cognition derives from the brain, this self-organized activity is its most likely source. Ensemble synchrony of neurons should therefore reflect the combination of some selected physical features of the world and the brain's interpretation of those features. Even if the stimulus is invariant, brain state is not. From this perspective, the most interesting thing we can learn about the brain is how its self-generated internal states, the potential source of cognition, are brought about. Extracting the variant, that is, brain-generated features, including the temporal relations among neuronal assemblies and assembly members, from the invariant features evoked by the physical world might provide clues about the brain's perspective on its environment. Yet, this is the information we routinely throw away with stimulus-locked averaging.

Stochastic Resonance

The optimal performance of man-made devices can be notoriously deteriorated by the presence of noise. But noise is not necessarily bad. An oft-quoted beneficial aspect of noise in bistable systems, for example, neurons, is its ability to amplify hidden periodic signals under certain conditions. Consider a rhythmic input to a neuron that produces depolarization at regular intervals but always below threshold. Because the neuron does not spike, its oscillatory state is not informed to downstream neurons. However, if a neuron also receives a Gaussian (white) noisy input, which alone would not discharge it, the noise and the periodic signal add up, resulting in an occasional action potential, timed by the depolarizing phase of the input. This signal combination is known as stochastic (probabilistic) resonance (figure 6.5). It is a phenomenon where a weak signal is detected or transmitted optimally in the presence of noise. Because it is unpredictable when the combination of the random noise and the periodic signal supersedes the threshold, the output spikes will occur seemingly randomly. In effect, the noise removes the apparent predictability of the oscillation. However, analyzing large-enough intervals between spikes, the statistical distribution of spike intervals can identify an underlying periodicity at the same frequency as the input. In this simple example, noise can help convey the signal through the neuron by facilitating its spiking. This is the main reason why noise can maintain spontaneous activity in computer models of neural networks. Signals become detectable due to resonance between the weak deterministic signal and stochastic noise. Stochastic resonance thus appears as a mechanism for extracting information from weak periodic signals. Although rhythmic stimuli are ubiquitous in all sensory modalities, nonrhythmic, time-varying inputs can be detected by the same principle.

Stochastic resonance epitomizes noise-controlled onset of order in a complex system in many fields of natural science. In the brain, stochastic resonance can be useful for not only single cells but also for communication between cell assemblies

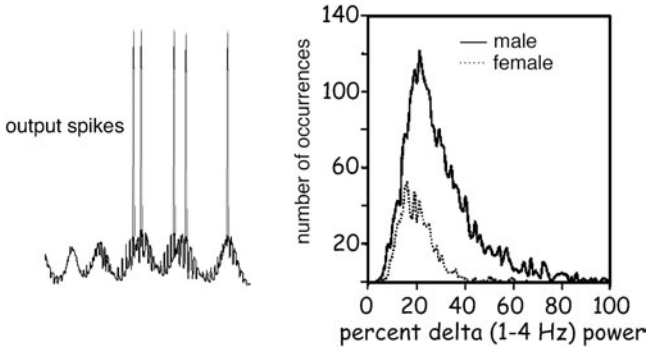

Figure 6.5. Input feature extraction by stochastic resonance. Left: Combination of slow and fasts oscillations can discharge a single neuron, when neither the fast nor the slow oscillatory inputs alone can. The output spike patterns contain information about the frequencies of both inputs even if it occurs irregularly. Right: Stochastic resonance at the systems level. Probability of occurrence of high-voltage spindles (y-axis) in the neocortex of the rat is highest at a preferred magnitude of delta power in the preceding 2 seconds. The parabolic relationship between the event probability and delta power magnitude is the hallmark of stochastic resonance. Modified, with permission, from Jandó et al., 1995.

or large systems within the brain. As discussed in the following Cycles, oscillatory behavior in cell groups, modules, structures, and systems is state and context dependent. Information from one place to another is transferred in small temporal packages on a certain phase of the oscillatory cycle. A mechanism selectively tuned to extract such messages and deduce the metric of the intrinsic dynamics of the sending assembly is of great importance. This is where stochastic resonance may be beneficial for neuronal systems.

As one might expect, the amount of noise is critical for the proper amplification of the signal: too little noise and the signal does not get through, whereas for larger noise amplitudes the signal increasingly gets corrupted. This noise-based optimization is the essence of stochastic resonance. Noise can be added to the signal externally or internally by the brain.[29] Although the term "stochastic resonance" is the invention of physicists, the concept is quite familiar in psychology and is known as the Yerkes-Dodson law, which describes an inverted U-shaped function between arousal and performance. A corollary is that there are optimal

29. The simplest stochastic resonant model is represented by a symmetric bistable process $x(t)$ driven by the combination of an external sinusoidal modulation and an additive random noise. The amplitude of the periodic component of the process, x, grows sharply with the noise intensity, and after its maximum it decreases according to a power law (Benzi et al., 1981; Bulsara and Gammaitoni, 1996). The parabolic relationship of noise magnitude (inverted U-shaped curve) on signal detection is the hallmark of stochastic resonance (Wiesenfeld and Moss, 1995). For examples of the beneficial effect of external noise in models and perception, see Ward (2001).

levels of arousal for each task to be learned.[30] Viewed from the present context, an important mechanism at work in arousal is stochastic resonance, an amplification of incoming signals by added neuronal noise.

Although signal amplification through noise appears advantageous for the brain, it has its own problems. A critical issue is the source of noise. Classical theories, in which the brain is viewed as a stimulus-driven device, assumed that spike response variability in response to an invariant input derives from unreliable individual neurons.[31] According to such view, a neuronal population can represent consistent and coherent decisions, but single cells within the population can cast different votes. These individually incongruent opinions are usually regarded as wasted action potentials from the representational point of view and are considered the source of synaptic noise. From the "population code" perspective, stochastic resonance is a clever mechanism because it can "recycle" the wasted action potentials. However, in contrast to the population code model, numerous recent works emphasize that action potentials are used sparingly in the brain, and spiking of neurons is much more reliable than previously thought.[32] If spikes are used efficiently in the brain, then what is the source of noise that seems so critical for the maintenance of spontaneous brain activity? Furthermore, if the brain has to regulate its own noise level to enhance input sensitivity, noise utilization is not so attractive anymore.[33]

The issue of noise generation invokes a broader theoretical problem. Finite fractional dimension and the resultant scale-free behavior are typically regarded as an indication of chaotic behavior.[34] The $1/f$ dynamics of EEG may be interpreted that there are dedicated brain mechanisms for the generation of pink noise. I suggest an alternative mechanism of noise production in the brain but with similar benefits: mixing of various oscillators. As discussed above, information stored in a given phase of the oscillatory output of one structure could be effectively read out by the target structure, provided that the faster oscillation in the

30. Yerkes and Dodson (1908).

31. In his challenge of the classical stimulus–response theories, Grossberg (1980) exploited the advantages of stochastic resonance in his "adaptive resonance" theory. In his model, the bottom-up and top-down pathways actively compare information and modify each other. A mismatch between centrally generated expectation and the input signal leads to attenuation of the afferent signal, whereas a match amplifies its propagation.

32. Single neurons can respond in a highly reliable manner both *in vivo* and *in vitro* (Mainen and Sejnowski, 1995; Kara et al., 2000; Buracas et al., 1998; Wehr and Zador, 2003; Fellous et al., 2004; Ikegaya et al., 2004). When spiking history (Henze and Buzsáki, 2001) and peer neuron firing effects (Harris et al., 2003) are taken into quantitative consideration, precise spike timing is revealed even when neurons are embedded in complex interconnected networks (Riehle et al., 1997). For the computational advantage of sparse coding, see Levy and Baxter (1996).

33. Noise in the brain has yet to be shown to be controllable in ways useful for its operations (Kelso, 1995). For an effect of stochastic noise on single-cell models, consult Ho and Destexhe (2000); on small networks, see Gluckman et al. (1996).

34. Distinction between deterministic chaos and noisy quasi-periodic systems is not straightforward because in many cases their macroscopic behavior is equivalent (Rapp et al., 1993; Kelso, 1995; Glass, 2001).

target is phase-locked to the input and the combination of the two oscillators sufficiently depolarizes the neurons. Recall that the only function of noise in stochastic resonance is to increase the magnitude of input variability so that the subthreshold periodic input occasionally becomes effective in discharging some of the target neurons. If so, this critical role can be played by a transient faster oscillation, instead of white noise. Ample empirical evidence is available for transient coupling between an oscillation in one structure and a faster oscillation in another, a topic I discuss in more detail in Cycle 12. With such oscillatory coupling, extraction of phase-coded information can be efficiently exploited by taking advantage of the mechanism of stochastic resonance without getting into the trouble of generating metabolically costly noise. Viewed from this perspective, dynamic coupling of neuronal oscillations as a source of noise should be regarded as a beneficial brain operation even for the most ardent opponents of brain rhythms.

Experiments in animals and humans support the idea that the brain exploits stochastic resonance. Examination of the relationship between background EEG activity and the probability of occurrence of epileptic patterns in rats revealed a parabolic relationship. Maximum probability of the abnormal pattern is associated with a narrow range of delta power in the 2 seconds prior to the events, whereas the probability decreased when delta power either increased or decreased (figure 6.5, right). The parabolic relationship between the signal detection and noise magnitude is the hallmark of stochastic resonance. The ongoing EEG also has a definite relationship with psychophysical performance. When subjects were requested to detect near-threshold tactile stimuli on the tip of their index finger, the best performance was observed when the power of the prestimulus alpha oscillation assumed intermediate values in the somatosensory cortical area.[35] The "optimum" level of noise in the jargon of stochastic resonance may be the brain's solution to the so-called "baseline shift" problem of perception[36] and motor activity precision and supports the long-held wisdom that "proper" level of brain activity is needed for optimizing behavioral performance.

Emergence of Cell Assemblies through Synchrony

Donald O. Hebb was among the first thinkers who explicitly stated that the brain's ability to generate a coherent thought derives from the spatiotemporal orchestration

35. The animal experiments were done by Jandó et al. (1995). There are many physiological explanations available for explaining the "optimum" noise that results in an inverted U-shape level of activity, including voltage-gated channels and competition between receptors with opposing actions for the same neurotransmitter. For experiments in humans, see Collins et al. (1996) and Klinkenkaer-Hansen et al. (2004).

36. A concise summary on the baseline problem of performance is Drive and Frith (2000). For a discussion of the baseline problem in the imaging (PET, fMRI) fields, see Gusnard et al. (2001).

of its neurons, which we refer to as the "cell assembly" hypothesis.[37] Hebb's cell assembly is a transient coalition of neurons, much like the dynamic interactions among jazz musicians. Members of the cell assembly are brought together by Hebb's synaptic plasticity rule, on the basis of temporal relations among them: "*When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.*"[38] As a result of this plasticity rule, information reverberates within the formed assembly and the direction of flow is determined by the synaptic strengths among the members. Three hypothetical features are inherent in the cell assembly hypothesis. First, activity within a cell assembly is synchronized more than predicted by the sensory input because neurons are interconnected and influence each other. For the cell assembly hypothesis, the trial-to-trial variability of spike trains is not a surprise, since the activity of a single cell is supervised by the group of which the neuron is a part. Second, Hebb believed that activity reverberates in loops of synaptically connected chains of neurons. This reverberation explains why activity can outlast the physical presence of an input signal. In the language of engineers, this refers to hysteresis, a reflection of nonlinearity in the system.[39] Third, assembly membership is flexible, so that a given neuron may be part of several assemblies (figure 6.6). Of course, not every conceivable coincidental firing of neurons meets the criterion of an assembly formation. Membership must be reflected by a statistically reliable synchrony beyond chance.

Although much of contemporary cognitive neuroscience is based on Hebb's loosely defined broad postulates, experimental verification of his ideas had to wait until the recording of large populations of neurons became possible in behaving animals. Indirect support, however, has been available since the 1970s. E. Roy John at New York University trained cats in a signal discrimination situation. For example, the cats learned to respond to a 4 hertz but not an 8 hertz visual or

37. Hebb (1949). Hebb's concept has been advanced and refined by Braitenberg (1978) and Abeles (1982). Similar ideas emerged independently in the Soviet movement control group. Nikolai Bernstein's school broke away from the hard-wired view of muscle control and, instead, suggested the emergence of flexible neuronal groups that are temporarily assembled to solve specific control tasks. Bernstein hypothesized that movements result from the virtually infinite variety of possible combinations, or degrees of freedom, of neuromuscular and skeletal elements. Each movement pattern is considered to be a self-organized event assembled from the flexible partnership of the controlling neurons. Sequential activation of the various muscle groups of a limb is coordinated by different sets of neurons active on different phases of a central oscillator. This idea is quite similar to Hebb's notion of ensemble sequences. Bernstein's most influential book, *On the Construction of Movements* (*O Postroyeniis Dvizheniy,* Medgiz, Moscow, 1947), was translated to English 20 years later (Bernstein, 1967). See also Gelfand et al. (1971) and Whiting (1984).

38. Hebb (1949, p. 62; italics original). This critical temporal relationship, considered one of Hebb's most important intuitions, has been known since the days of Ivan Petrovich Pavlov. The essence of Pavlovian conditioning is that the conditional signal must consistently and repeatedly precede the unconditioned signal to bond an association so that the conditional signal can repeatedly and consistently take part in evoking the unconditioned response (Pavlov, 1927).

39. In physical systems, hysteresis (Greek for deficiency) refers to history dependence.

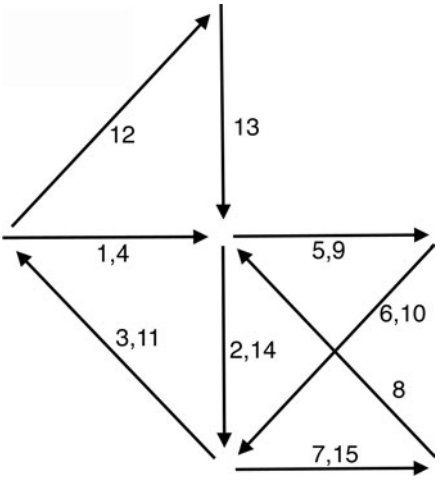

Figure 6.6. Schematic of Hebb's reverberating cell assemblies. Arrows represent not single neurons but an "assembly" of neural pathways or open multiple chains firing according to the numbers on each. The same assemblies can participate more than once (e.g., pathway 1,4 indicates that this subassembly of neurons fires first and fourth). The direction of flow is hypothesized to be determined by the synaptic strengths within and across assemblies. However, without inhibition or other means to restrain excitatory activity, progressively larger groups of neurons and assemblies would be engaged, rather than reactivating the same chain of 15 subassemblies repeatedly. Reprinted, with permission, from Hebb, (1949).

auditory stimulus. John and his colleagues observed that the evoked field responses in many brain areas contained a component that was specific to the behavioral consequences rather than the physical features of the stimulus. They called this component "readout from memory," referring to the idea that this modality-independent and widely distributed signal represented the "decision" made by the animal on the basis of previous experience. A key aspect of their work was the relationship between the "readout" component and behavior at times when ambiguous stimuli (e.g., 6 hertz) were presented or when the animal made an error. As predicted by the assembly hypothesis, the statistical features of the readout component reflected whether the cat responded rather than the physical features of the signal, indicating that distinct patterns can be released from memory.[40]

With the ability to record simultaneously from representatively large numbers of cells from the hippocampus, we set out to test the cell assembly predictions directly. Jozsef Csicsvari, Hajime Hirase, and George Dragoi working in my lab have already collected a large database in behaving rats. The receptive fields of hippocampal neurons are characterized by the animal's position in the environment (see

40. John (1968) and John and Morgades (1969).

Cycle 11). Monitoring only the motor behavior of the animal, the best prediction one can make about the precise temporal occurrence of spikes in single cells can be made only from the momentary position of the rat.[41] However, on some seemingly identical trials, a place cell can fire vigorously, whereas on others it remains silent. Ken Harris and I reasoned that, if hippocampal cells are organized into cell assemblies, then members of the assembly can provide information not only about *whether* a chosen recorded neuron fires but also *when,* with a temporal precision that is better than can be inferred from the animal's overt behavior (figure 6.7).

The key aspect of the experiment was a novel statistical test that Harris developed and dubbed the "peer prediction method." For each recorded neuron, the timing of its spikes can be predicted by the behavior of the animal with some precision. If spike occurrence and timing are determined solely by variables external to hippocampus, information about the other simultaneously recorded neurons would not make any difference. On the other hand, if other assembly members are present in the recorded population, information about their activity should improve prediction, commensurate with the proportion of assembly members recorded. Harris's clever analysis showed that adding information about the temporal structure of the population to the behavioral data can drastically improve the prediction of an apparently stochastic spiking pattern. Importantly, this improvement derived not only from neurons with correlated spiking but also from neurons that were specifically silent at times when the selected target neuron emitted a spike. Thus, the explicit absence of spikes (anticorrelation) is as important as the spiking activity of assembly members. In a separate set of experiments, Dragoi demonstrated that membership in cell assemblies is indeed modifiable by altering synaptic connectivity among the neuronal population. Together, these findings provided quantitative evidence for Hebb's intuition about neuronal assembly organization 50 years ago.[42]

The greatest strength of Hebb's cell assembly hypothesis—simplicity—is also its weakness. A cell assembly is defined as group of cells with excitatory connections whose synapses have been strengthened by coactivation and whose excitatory connections are stronger among themselves than with other nonmember neurons. There are many postulated cell assemblies, and activity can hop from one assembly to the next. The boundaries of assemblies are implicitly determined by the hypothetical groups of anatomically connected neurons that fire together. However, with excitatory neurons only no segregation of assemblies is possible. As discussed in Cycle 3, without inhibitory interneurons, excitation produces only further excitation. Without inhibition, activity can spread from one assembly to the next, and the whole brain would be synchronized by an external stimulus every time the stimulus is applied. So how does the activity stop? Hebb's assembly hypothesis has no answer, because it contains no mechanism for flexibly

41. Hippocampal patterns and place cells are discussed in Cycle 11.

42. Harris et al. (2003a), Harris (2005) and Dragoi et al. (2003). Experiments by Wolf Singer and colleagues in the primary visual cortex have already provided indirect evidence that neurons can be part of one or more assemblies, depending on the conditions (e.g., Engel et al., 1991).

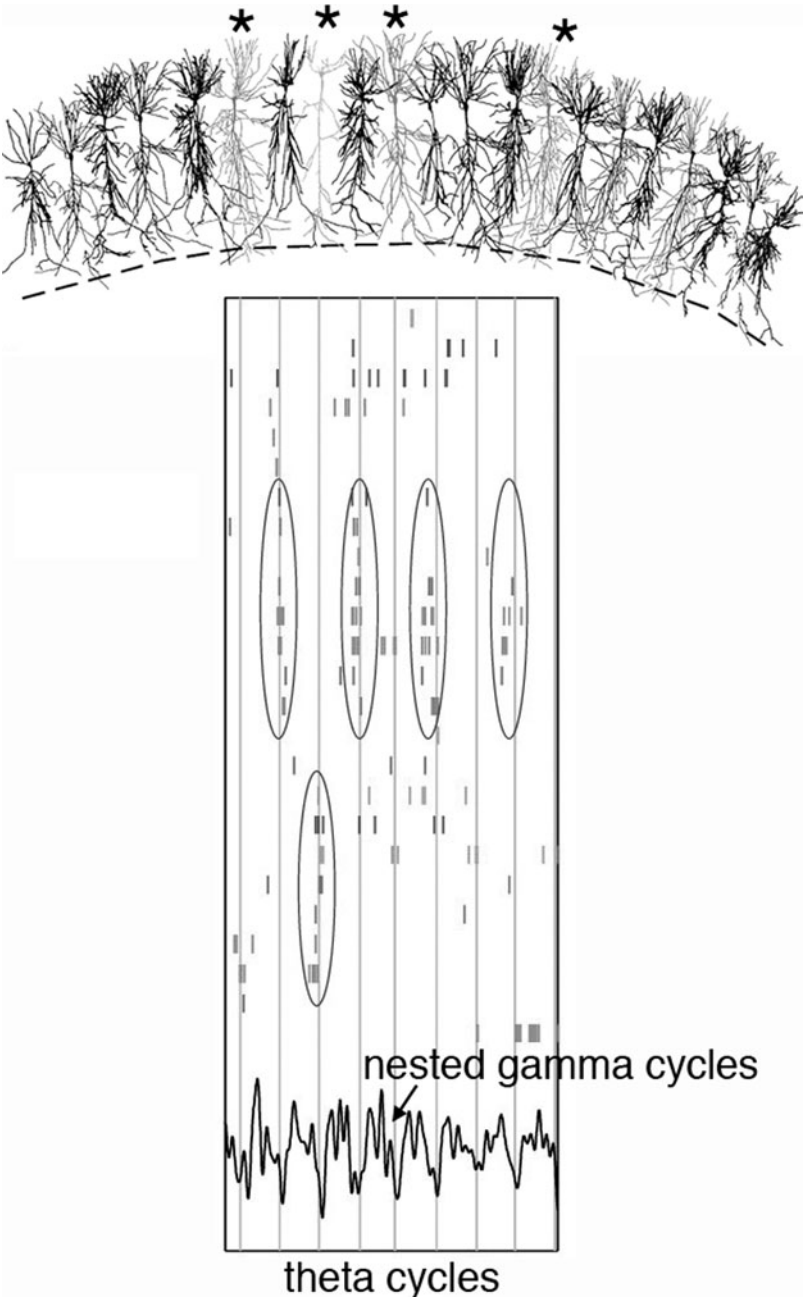

Figure 6.7. Cell assemblies are organized by oscillatory timing. In the hippocampus, pyramidal neurons without synaptic connections can come together repeatedly at the trough of theta oscillation, with the precision of nesting gamma cycles. Through temporal organization, cell assemblies can exert a maximal impact on their downstream, common target neurons. Modified, with permission, from Harris et al. (2003).

engaging and disengaging cell assemblies for entering and transferring information: it does not have a temporal metric.[43] The beginning of assembly activity is signified by an external stimulus, but there is no postulated mechanism that would terminate sequential activation of all possible assembly combinations or time a motor event by synchronous neuronal discharge. Without properly timed inhibition, cell assemblies can produce only avalanches (Cycle 3). Furthermore, according to Hebb's definition and that of several subsequent investigators, a prerequisite for cell assembly organization is the existence of excitatory connections among assembly members.[44] This definition excludes a very large population of neurons of the cortex and, in fact, many other parts of the brain where neurons are not connected directly by excitatory synapses. Yet, because neurons can be brought together flexibly in time by inhibition or by common inputs, these dynamically created groups can exert the same selective effect on their distributed and specific joint targets as Hebb's postulated assemblies, which are held together by excitation.

Armed with the peer prediction method, we were able to ask perhaps the most intriguing question about cell assemblies: what is their temporal scale? By varying the time window within which spike times of the chosen target neuron were predicted from the recorded population, the most effective time window could be calculated. For our hippocampal population, this optimal window turned out to be between 10 and 30 milliseconds. The time scale of the cell assembly may be of particular functional significance because many physiological variables share this time window.[45] Of these, the time constant of the pyramidal cells is perhaps the most important, because this is the window that determines a cell's integration ability. Importantly, the assembly window also matches the time period of gamma-frequency oscillations (Cycle 9). We can therefore conclude that cell assemblies are synchronized within the time window of gamma oscillation periods

43. Later versions of Hebb's cell assembly hypothesis (Braitenberg, 1978; Abeles, 1982) also lack defined temporal scales. In these works, a cell assembly is generically defined as group of interconnected cells whose synapses have been strengthened by coactivation. Because a single neuron can be part of several assemblies, the probability of finding routes between assemblies through joint members is likely very high. Thus, the size of a cell assembly, defined by preferred connectivity between neurons, is large and, in principle, involves the whole cerebral cortex. In a feedforward or synfire chain (Abeles, 1982), activity patterns can spread across the entire network. The larger the network is, the larger the cell assembly. However, engaging the entire network of growing synfire chains requires progressively longer time, a serious limitation of very large networks. Importantly, in more realistic, three-dimensional synfire networks (i.e., no longer a chain), the activity can reverberate forever.

44. Braitenberg (1978), Abeles (1982), Palm (1982), and Miller (1996a,b).

45. Duration of excitatory postsynaptic potentials in pyramidal cells *in vivo* is also in the 10–30 millisecond range. Furthermore, this temporal window is most critical for spike-timing–dependent plasticity of synapses (Magee and Johnston, 1997; Markram et al., 1997; Bi and Poo, 1998). Layer 4 cortical neurons show a resonance and subthreshold oscillations in this time period (Pedroarena and Llinás, 1997), and their resonant properties make them especially sensitive to inputs at this frequency. Note that in our formulation of assembly function, the population firing rate in a given time window (i.e., assembly synchrony) is the important variable, independent of whether it is achieved by a strict rate or temporal "coding" mechanism (Harris et al., 2003a; Harris 2005).

because this allows an assembly to exert the largest possible impact (i.e., depolarization and discharge) on their downstream targets.

Our temporal definition of cell assemblies is therefore different from the strict connectivity-based definition of Hebb. If neurons are brought together within a critical temporal window, it is immaterial for a target observer neuron whether the presynaptic neurons are connected. Just as synchrony is defined by the observer, cell assembly formation is also an observer-centric process. Nevertheless, if the presynaptic neurons are also connected, their synchronous discharge may strengthen their synaptic communication, as predicted by Hebb's plasticity rule. Because of the interdependence of the neurons, self-organized assembly patterns enhance cohesion among its members by restricting their degrees of freedom. This higher order organization provides their identity. Neurons discharging at different times can be part of many assemblies. The uniquely changing assemblies in each oscillatory cycle can target anatomically unique sets of neurons. Through assembly organization, time is translated to neuronal network space.

Integration, Segregation, and Synchrony: Is There a Balance?

Complexity and synchrony compete with each other. Therefore, in networks with finite size, synchrony increases at the expense of complexity. Cortical networks have both feedback and feedforward components, and they complement each others' function. Feedback excitatory connections can maintain activity in a restricted place and even restore fragmented information, for which reason they are also called autoassociative networks.[46] In contrast, feedforward connections are effective in propelling the information progressively in one direction. At first approximation, sensory-related information is processed in feedforward networks, whereas brain-added information arises in recurrent networks.

Because separation of signal sources in the intact cortex is so difficult, computer models have been designed to study their operations in isolation. Abeles's "synfire chains" have been specifically designed to examine how the input is progressively processed as activity travels forward in different layers and assemblies. A major weakness of feedforward only systems is that, once an error enters at any level, it is propagated and amplified in downstream layers, just like the useful signal. The nature of the mechanism that provides the safest information transfer in multiple layers is not known.[47] One proposal is that the key variable is the firing rate of neurons, because rate determines the overall depolarization, and consequently the discharge, of the target neurons. An alternative view is that synchrony

46. Kanerva (1988) is an excellent introduction to autoassociative networks.

47. In synfire chain models, autoassociative circuits, superimposed on the feedforward architecture, can serve to provide error corrections (Abeles, 1982). Salinas and Sejnowski (2001) and Vogels et al. (2006) also discuss the importance of the balance between excitatory and inhibitory forces for stable propagation of information.

is of primary importance in the transmission of temporally precise signals. These competing ideas are sensitive to both network architecture and the biophysical properties of its constituent neurons, so it does matter how neurons are modeled in the networks.

Because of convergence and divergence of the projecting neurons to a subsequent layer, the target neurons will inevitably share some of the same synaptic inputs. The denser the connections are, the larger the probability for joint inputs. These common inputs tend to discharge their downstream targets within a narrow time window. The synchronous output from the target neuron can synchronize even more neurons in subsequent layers, unless synchrony is specifically prevented. Although specific features of neurons often become critical in the synchronization process,[48] in the first pass, one can avoid the many assumptions of single-neuron models. Alex Reyes from New York University just did that by designing a feedforward hybrid of computer network and real, *in vitro* recorded neurons. Feeding white noise into a single layer 5 neuron, say, 1,000 times, he obtained 1,000 different outputs. He treated these outputs as if they were emitted by 1,000 different neurons in his first layer and used them to generate another 1,000 outputs in the second layer, and so on. Even though he used only a single neuron repeatedly or, occasionally, two or three neurons, he created a multiple-layer feedforward network, consisting of many identical but real neurons. His consistent finding was that, even though the network was fed with a Poisson (random) input, synchronous oscillations developed in subsequent layers under a wide range of conditions and network configurations. Because his networks resisted manipulations that were designed to destroy synchrony, Reyes concluded that synchrony is the default state of feedforward cortical networks.

Can real cortical networks avoid such default synchrony? One obvious criticism of the Reyes's approach is that, in real networks, neurons are not identical. This cannot be the single answer because synchrony did not change much when he used different neurons, which presumably were sufficiently different from each other. Another argument is that, in the model, the neurons were discharged by current injection into their cell bodies, instead of physiological dendritic excitation. A third criticism is the limited number of convergence relative to the *in vivo* situations. Although these factors are likely important to some degree, they are probably not critical. As discussed in Cycle 5, the default state of cortical networks, operating with glutamatergic excitatory and GABAergic inhibitory synapses alone, is synchrony, independent of its size. Only in the presence of subcortical neurotransmitters can cortical networks operate in the "critical state" to generate the highest degree of complexity. Otherwise, they just synchronize and pause.

Synchrony in response to shared inputs might be an important factor behind the now classical observation of David Hubel and Torsten Wiesel. Their key

48. For a debate on rate vs. temporal coding of information, consult Barlow (1972), Gray (1994), Buzsáki et al. (1994a), Konig et al. (1996), Shadlen and Movshon (1999), Shadlen and Newsome (1999), and Engel et al. (2001). For the critical role of the biophysical features of single neurons in oscillatory network synchrony, see Golomb and Hansel (2000).

finding was that, if a neuron responded to a particular shape and movement of the visual stimulus, other neurons in the same vertical penetration tended to behave similarly. These observations provided strong ammunition for the columnar organization idea of the neocortex.[49] Nevertheless, a major caveat of these observations is that they were all done under anesthesia, with the effects of subcortical inputs severely attenuated, and using relatively simple stimulus configurations.

As just discussed, isolated cortical networks are especially susceptible to neuronal synchronization, but this susceptibility is not always advantageous or physiological. An inevitable consequence of connection divergence of inputs and the primarily local organization of neocortical networks is that neighboring neurons share similar information because they share similar inputs. This redundancy at first appears to be a useful security mechanism. If a few neurons fail to respond to the inputs, their peers may still transfer the information. However, given the high metabolic demands of neuronal operations, such redundancy may be very costly. Moreover, feedforward and feedback excitatory pathways tend to recruit very large populations of neurons, such that a single message can engage a considerable part of the network. Obviously, such redundancy seriously compromises the amount of information that can be processed by a given size network. Indeed, recent experiments indicate that such redundancy, in most part, is due to anesthesia and the testing conditions.[50]

Barry Richmond and colleagues at the National Institute of Mental Health tested behaving monkeys with stimuli of varying complexity. When simple bars and edges were used as stimuli, as much as 40 percent of the signal variance of one neuron was related to that of an adjacent cell, a high level of redundancy. However, when responses to more complex two-dimensional patterns were analyzed, the shared variance dropped to 20 percent. Although no true natural stimuli were tested, the findings suggest that functional segregation among local principal cells increases with input complexity. Importantly, these investigators also found that the degree of independence between adjacent neurons increases with input complexity in both primary visual cortex and inferior temporal cortex, the first and last stages of visual processing.[51] These novel observations argue in favor of

49. Hubel and Wiesel (1963). For columnar organization of the cortex, see Szentágothai (1978) and Mountcastle (1997).

50. The relatively independent operation of principal cells is a prerequisite of representing flexible associations in the outside world. As discussed in Cycle 3, this freedom is mainly provided by the inhibitory interneuron system.

51. Gawne and Richmond (1993) and Gawne et al. (1996). DeAngelis et al. (1999) also found that, when receptive field properties of neighboring neurons in the primary visual cortex (V1) were measured with high precision, the overlap was more of an exception than a rule. While intracolumnar processing of information is generally considered to be the most fundamental operation of the cortex, it is ironic that cortical columns are defined by their uniform response properties. This paradox could be due to biased and unsorted neuronal recordings in the cortex. Neurons and their properties in different cortical layers are rarely distinguished (Krupa et al., 2004). Likewise, the information embedded in the fine temporal order of neurons is only rarely considered (Reich et al., 2001).

a general organization principle for independent information processing by members of local neuronal groups throughout the cortex.

Although the exact mechanisms of such redundancy-reducing effects are not known, a potential mechanism of functional segregation of principal cells is activity-dependent inhibition (Cycle 3). The segregation and grouping services of interneurons are not simply due to inhibition but to a nonlinear interaction between the excitatory and inhibitory population. Furthermore, as discussed above, the resonant-oscillatory features of interneurons allow them to select inputs based on their frequency characteristics. Due to such intrinsic biophysical features, the effectiveness of the spike-transmission probability varies as a function of the firing frequency of the presynaptic pyramidal cell. For example, in the hippocampus, spike transmission from pyramidal cell to interneuron is low at both low and high frequencies and highest at 15–40 hertz, which is the typical discharge frequency of an activated pyramidal neuron. In other words, a single but strongly "activated" pyramidal cell can exert an equal or larger effect in discharging its basket neurons than several dozen other presynaptic neurons discharging the same number of spikes because they target different, rather than the same, synapses. In essence, the high-frequency discharge of a pyramidal cell in its receptive field "enslaves" its basket cells through resonance tuning. In turn, the output of the basket cells suppresses the activity of the surrounding pyramidal neurons.[52] Such "winner-take-all" or "rich-gets-richer" mechanisms are abundant in complex systems, from automatons to Bill Gates's empire, and analogous mechanisms may be responsible for the segregation of neurons in networks strongly interconnected by excitatory collaterals.

Experiments in the visual cortex by Yves Fregnac and colleagues at the Centre National de la Recherche Scientifique, Gif-sur-Yvette, France, further support the role of inhibitory circuits in enhancing neuron segregation in local circuits. Inhibition and excitation are generally thought to be perfectly balanced. While inhibitory/excitatory balance maintains stability in neuronal networks at longer time scales, large discrepancies often occur transiently. For example, perfect balance in the visual system would imply that excitation and inhibition are strongest at the cell's preferred orientation and weakest at the nonpreferred orientation, but balanced in both cases. In contrast, when Fregnac and colleagues systematically assessed the relative contribution of excitatory and inhibitory inputs, they found diversity for stimuli moving in different directions. In some neurons, inhibition appeared strongest at directions orthogonal or opposite to maximum excitation.[53] A possible explanation of these findings is that principal cells with different orientation sensitivities compete for their common interneurons. In turn, interneuron

52. Marshall et al. (2002).

53. Monier et al. (2003). In the somatosensory cortex, timing of inhibition plays a critical role in the tuning of stimulus direction selectivity of layer 4 stellate cells (Wilent and Contreras, 2005). In the hippocampus, the ratio of excitation and inhibition varies as a function of the theta cycle in pyramidal cells. During sharp wave/ripple events, excitation transiently exceeds inhibition by as much as threefold, providing short temporal windows for facilitating somatodendritic spike propagation and synaptic plasticity (Csicsvari et al., 1999; King et al., 1999).

networks can bias the effective local connectivity and segregate adjacent principal neurons. In doing so, they reduce the redundancy between principal cells and maximize the amount of information transmitted by the principal-cell population. Inhibitory interneurons are therefore the key players in the integration and segregation process by allowing or preventing synchrony and bringing together or separating principal cells in time.

Oscillatory Synchrony Is Energetically Cheap

The paramount advantage of synchronization by oscillation is its cost-effectiveness. No other known mechanism in the physical world can bring about synchrony with so little investment. What do I mean by declaring that synchrony by oscillation is cheap? Let me illustrate the cost issue first with a few familiar examples from our everyday life. You have probably watched leisurely strolling romantic couples on a fine evening in a park or on the beach. Couples holding hands walk in perfect unison, whereas couples without such physical links walk out of step. You can do this experiment yourself. Just touching your partner's finger will result in your walking in sync in a couple of cycles. Unless your partner is twice as tall or short as you, it costs pretty much the same effort to walk in sync as out of sync. Once you establish synchronous walking, it survives for quite some time even if physical contact is discontinued. If both of you are about the same height and have a similar step size, you will stay in sync for a long distance. In other words, synchronization by oscillation requires only an occasional update, depending on the frequency differences and precision of the oscillators. Two synchronized Patek Philippe vintage timepieces can tick together for many weeks, and quartz watches fare even better.

A much larger scale example of synchrony through oscillation is rhythmic clapping of hands, an expression of appreciation for superior theater and opera performances in some countries. Clapping always starts as a tumultuous cacophony but transforms into synchronized clapping after half a minute or so. Clapping synchrony builds up gradually and dies away after a few tens of seconds. Asynchronous and synchronous group clapping periods can alternate relatively regularly. An important observation, made by Zoltán Néda at the Babes-Bolyai University, Romania, and his colleagues, is that synchronized clapping increases the transient noise during the duty cycle, but it actually diminishes the *overall* noise (figure 6.8).[54] The explanation for the noise decrease during the synchronized clapping phase is the simple fact that everyone is clapping approximately half as fast during the synchronous compared with the nonsynchronous phase. Oscillatory entrainment nevertheless provides sharp surges of sound energy at the cost of less overall muscular effort. The waxing and waning nature of rhythmic

54. Neda et al. (2000). Most of the observations were taken in the small underground Kamra (Chamber) Theater in Budapest.

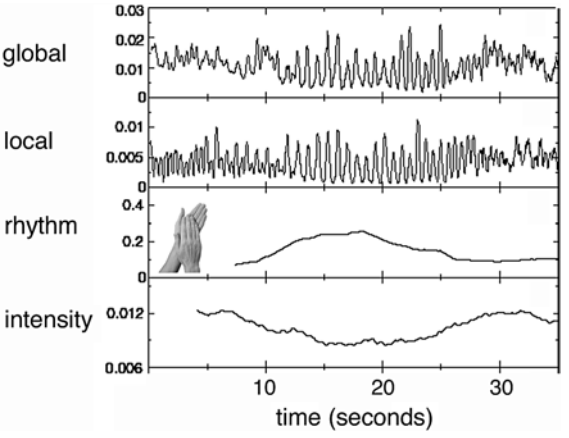

Figure 6.8. Emergence of synchronization in population hand clapping. Global and local noise was measured by microphones above the audience and placed next to a spectator, respectively. Rhythmic group clapping emerges between 12 and 25 seconds. Average global noise intensity, integrated over 3-second time windows, indicates *decreased* energy spending by the audience during the rhythm despite large surges of noise. Reprinted, with permission, from Neda et al. (2000).

hand clapping is reminiscent of numerous transient oscillatory events in the brain, especially in the thalamocortical system. Similar to hand clapping, the total number of spikes emitted by the participating neurons and the excitatory events leading to spiking may be fewer during these brain rhythms than during comparable nonrhythmic periods. A direct test of this hypothesis would require simultaneous recordings from large numbers of individual neurons. Indirect observations, using brain imaging methods, however, support the idea.[55]

Perhaps the most spectacular example of low-energy coupling, known to all physics and engineering majors, is the synchronization of Christiaan Huygens's pendulum clocks. Huygens's striking observation was that when two identical clocks were hung next to each other on the wall, their pendula became time-locked after some period. Synchrony did not happen when the clocks were placed on different walls in the room. Huygens's clocks entrained because the extremely small vibrations of the wall that held both clocks were large enough that each rhythm affected the other. The physical reason for synchrony between *two* oscillators is relatively simple, and solid math exists to explain the phenomenon.[56] However,

55. The BOLD signal (see Cycle 4) decreases over large cortical areas during both alpha dominance (Laufs et al., 2003) and thalamocortical spike-and-wave epilepsy (Salek-Haddadi et al., 2002), demonstrating that the metabolic cost of neuronal activity associated with increased neuronal synchrony may, in fact, be less than during nonrhythmic states.

56. For the English translation of Huygens's original letter about the "sympathy" of clocks, see Pikovsky et al. (2001).

extrapolation from two oscillators to the coupling behavior of large numbers of oscillators is not at all straightforward. Imagine that, in a cylinder-shaped room, 10 clocks are placed on the wall equidistant from one another, each started at a different time. In a second, much larger room, there are 100 clocks. Finally, in a giant arena, we hang 10,000 identical clocks on the wall. As with Huygens's two clocks, each clock in the rooms has neighbors on each side, and these clocks influence the middle clock. Furthermore, in the new experiment, there are many distant neighbors with progressively less influence. However, the aggregate effects of more distant clocks must be significant, especially if they become synchronous. Do we expect that synchronous ticking of all clocks will develop in each room? Various things can happen, including traveling waves of synchrony or local buildup of small or large synchronous groups transiently. Only one thing cannot occur: global synchrony.

I know the answer because we did an analogous experiment with Xiao-Jing Wang and his student Caroline Geisler. We built a network of 4,000 inhibitory interneurons.[57] When connectivity in the network mimicked local interneuron connections in the hippocampus, all we could see were some transient oscillations involving a small set of neurons (see figure 3.9). On the other hand, when the connections were random, a situation difficult to create in physical systems, a robust population oscillation emerged. So perfect harmony prevailed in a network with no resemblance to the brain but not with what appeared to be a copy of a local interneuronal network. The problem was the same as with the clocks on the wall: neurons could affect each other primarily locally. To reduce the synaptic path length of the network, we replaced a small subset of neurons with neurons with medium- and long-range connections. Such interneurons with medium- and long-range connections do indeed exist (see Cycle 3). The new, scale-free network ticked perfectly. Its structure shared reasonable similarities with the anatomical wiring of the hippocampus and displayed synchronized oscillations, involving each member equally, irrespective of their physical distance. The reason why our small-world-like artificial network synchronized is because it exploited two key features: few but critical long-range connections that reduced the average synaptic path length of the network and oscillatory coupling, which required very little energy. Analogously, cortical networks may achieve their efficacy by exploiting small-world-like organization at the anatomical level (Cycle 2) and oscillatory synchrony at the functional level. There is synchrony for (almost) free.

57. In reality, the issue we addressed was quite different from the clocks on the wall because none of the 4,000 interneurons was an oscillator. Instead, their interactions formed one single clock (Buzsáki et al., 2004). Couplings of numerous oscillators have been analyzed mathematically, but these mathematical models lack the physical constraints of axon conduction delays; therefore, they cannot be directly applied to coupling of brain oscillators (Kuramoto, 1984; Mirollo and Strogatz, 1990). For the coupling of two identical oscillators with realistic axon conduction delays, see Traub et al. (1996) and Bibbig et al. (2002).

Rules for Oscillatory Networks?

Can we use the knowledge learned from physics and engineering and apply it directly to neuronal oscillators? From the discussion above, one suspects that this may not always work effectively. The behavior of an isolated single neuron, being a relaxation oscillator, is strongly asymmetric with very short discharge (action potential) and long charge periods. However, when very large numbers of neurons come together with some time jitter, their integrated output, in principle, can be so smooth that the population may appear to behave like a sinusoid oscillator. In fact, this principle is routinely exploited by electric engineers to construct reliable sinusoid (i.e., harmonic) generators without the inconvenience of the inertia inherent in real sinusoid generators. The important implication is that some EEG rhythms with quasi-sinusoid appearance, such as the alpha waves of Hans Berger or hippocampal theta oscillations, can emanate from the relaxation oscillation features of single neurons. The critical issue to understand in the context of information transfer is whether the population behavior of these collective oscillators follows the rules of harmonic oscillators (as they appear macroscopically) or obeys the laws of relaxation oscillators, their elementary building blocks. In mathematics, one can conveniently classify oscillators into types, such as harmonic or relaxation or other names with properly defined equations.[58] Since each of the math-defined oscillators has distinct features and consequences from perturbations and synchronization, the experimentalist tries to explore the defining features of *in situ* oscillators and relate them to the off-the-shelf oscillators of mathematics and physics.

Unfortunately, network oscillations in the brain can be rarely equated with these models. The reasons for this are multifold. Despite the macroscopic appearance of almost sinusoid shape mean field for some rhythms, all brain oscillators known have differentiable duty and readiness phases, a key feature of relaxation oscillators. Neuronal spikes associated with field oscillators are typically grouped around the trough of the extracellularly recorded field, recorded near the somata of the principal cells that give rise to the rhythm. This correlation rule, independent of the oscillation frequency, arises from the facts that intracellular depolarization of the perisomatic region is reflected as an inward (negative polarity) current in the extracellular space and intracellular depolarization is associated with increased probability of spike generation (see Cycle 4). Based on this statistical relationship between the trough of the field and the spiking of pyramidal cells, one might conclude that inputs timed to the trough of the oscillation (i.e., during the duty cycle) might be less effective than inputs applied at the time of the

58. The review of these issues by the mathematician Nancy Kopell is an excellent summary of the analytical approaches to neuronal oscillators (Kopell, 2000). Another introductory review is Wang (2003). Single-neuron models are covered in Marder and Calabrese (1996). For a more comprehensive coverage of neuronal network oscillations, especially in their relation to epilepsy, I suggest Traub et al. (1999).

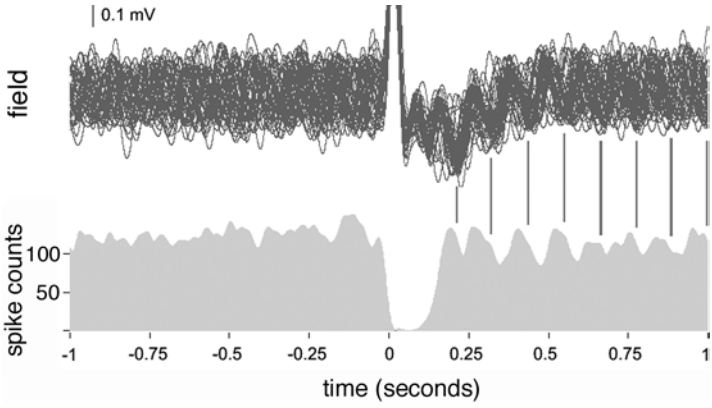

Figure 6.9. Single-pulse electrical stimulation of intrahippocampal afferents resets theta oscillation (field) and silences all spiking activity (spike counts) transiently. After reorganization, the field oscillation and concurrent neuron activity start at the same phase. Multiple superimposed traces show random phase distribution before but regularity after the stimulus. Note that the mean amplitude of the field and mean spike counts remains the same as prior to stimulation. This behavior is a telltale sign of a single global oscillator. Reprinted, with permission, from Zugaro et al. (2005).

peak. This is indeed the case when nearly all neurons fire in sync, such as epileptic discharges. However, in the physiological range of network operations, only a very small percentage of all neurons fire. Part of the remaining neuron population may also be depolarized but remain subthreshold, and yet another fraction may be hyperpolarized due to interneuron-mediated lateral inhibition from the discharging minority. Thus, an input synchronized to the trough of the field is less effective for two sets of neurons for two different reasons (i.e., spike refractoriness and hyperpolarization) but can be effective for the remaining subthreshold population. The magnitude of the response of an afferent input therefore depends on the portion of neurons being in the subthreshold readiness state, a feature that may vary from structure to structure and oscillation type. Similarly, an input timed after the duty cycle (e.g., the peak of the extracellular local field) may reset the phase of the population oscillation or remain ineffective because of interneuron-mediated feedback inhibition or because of intrinsic hyperpolarization in the discharging minority. These examples illustrate the disappointing "rule" of brain oscillators: coupling behavior depends on the details.

True relaxation oscillators are eager to synchronize during their readiness periods, but they need to be discharged in order to advance their phases. On the other hand, harmonic oscillators require very weak forces and can advance their phase incrementally. These defining features can be used to probe the nature of network oscillators. A simple test that can assess the property of an oscillator is its response to a transient perturbation, such as a single electrical shock (figure 6.9). The dynamics of the resumption of the original rhythm and the phase

dependence of the perturbation may provide information about the underlying mechanisms responsible for the network oscillation. An oscillator with relaxation properties should reset instantaneously. Because the population is constructed from heterogeneous individual oscillators with phase jitter, resetting the components into a common phase is expected to increase the size of the mean field.

Experiments on hippocampal theta rhythms showed that these oscillators do not obey the simple rules predicted by the known oscillators. Reset properties follow rules of the relaxation oscillator, yet phase reset does not affect the field amplitude. Theta network oscillators appear to behave as a single, "monolithic" oscillator even though they are made up of a very large and heterogeneous group of individual neurons.[59] The quasi-sinusoid field monolith of theta rhythm keeps time (phase) more precisely than the relaxation oscillations from which it is built. So here is another vague rule: the same macroscopic field can be brought about by numerous intrinsic cellular and network mechanisms, and accordingly, the resonant, transmission, and perturbation properties of the respective oscillators may be quite different. Seemingly identical architectures can either promote synchronization or resist it. Although I provide several examples of similarly behaving oscillators in later Cycles, to date, general rules are exceptional for brain oscillations. The coupling properties of the rhythmic networks should be determined experimentally in each and every case, aided by computer modeling.[60]

Briefly . . .

There are two requirements for an oscillator: opposing forces and positive feedback. Systems with opposing forces but without feedback can maintain only a transient oscillation with decreasing amplitude, a phenomenon called resonance. Neurons and networks with these properties preferentially treat inputs whose frequency matches their own resonance. Neuronal oscillators belong to the family of limit cycle or weakly chaotic oscillators. Two well-defined oscillators, harmonic and relaxation types, have numerous examples in the brain. Harmonic oscillators are good long-term predictors because their phase is constant. Relaxation oscillators can synchronize quickly and efficiently. Brain oscillators tend to

59. The phase reset behavior of hippocampal theta is a particularly good example of a brain rhythm that behaves like a single oscillator, even though it is built from several oscillator types (Zugaro et al., 2005).

60. Many different computer architectures can be built to mimic the same neurophysiological features. Here is a prime example: Prinz et al. (2004) simulated more than 20 million versions of a three-cell model of the pyloric network of the lobster stomatogastric ganglion using different combinations of synapse strengths and neuron properties. They found that virtually indistinguishable network activity can arise from widely disparate sets of underlying mechanisms, suggesting that many different combinations of synaptic strengths and intrinsic membrane properties can be consistent with appropriate network performance. However, only one or few of these are biologically relevant. As Paul Erdös also emphasized, of the many possible solutions, only the most elegant one(s) is in the "Book" (see Cycle 1).

exploit and combine these properties. Single neurons oscillate mainly because voltage-gated ion channels with opposite properties depolarize and hyperpolarize the membrane. Due to the differential distribution of the ion channels in the soma-dendritic domains, neurons can have multiple oscillatory and resonance properties. These properties can be tuned dynamically by either changing the neuron's input resistance or affecting open channel probabilities. Interneurons are especially prone to resonate and they are the primary building blocks for network oscillators.

Collective behavior of neurons is established through synchrony. Synchrony is a relative term, defined by the time within which some trace of an earlier event by an input is retained, which then alters the response to a subsequent event to other inputs. Events that can be integrated over time by the target neurons are synchronous. Although this temporal window is in the tens of milliseconds range for single neurons, oscillatory coalitions of neurons can expand the effective window of synchronization from hundreds of milliseconds to many seconds. Population synchrony enhances the effective output of the population and it can emerge also without the alternation of firing rates of individual neurons. Thus, synchrony by oscillation is a metabolically cheap mechanism to achieve a large impact. Neuron assemblies are formed as transient coalitions of discharging neurons with mutual interaction. Assemblies in the waking brain typically synchronize in the gamma frequency range. Assembly behavior is a consequence of self-organized interactions among neurons and this self-organization may be the source of cognitive function.

Stochastic resonance may be a mechanism for selectively extracting messages and deducing the metric of intrinsic dynamics of the sending assemblies. Instead of costly white (stochastic) noise generation, brain networks opted for transient coupling between oscillatory events of different frequencies with same benefits as stochastic noise.

Cycle 7

The Brain's Default State: Self-Organized Oscillations in Rest and Sleep

> Sleep that knits up the ravell'd sleeve of care,
> The death of each day's life, sore labour's bath,
> Balm of hurt minds, great nature's second course,
> Chief nourisher in life's feast.
>
> —William Shakespeare, *Macbeth*

Descriptions of brain functions and operations typically begin with the brain's responses to environmental inputs. Such an approach, often within the framework of information theory,[1] attempts to infer the mechanisms of neuronal processing from the brain's responses to invariant physical stimuli. However, the information theory strategy cannot account for important functions of the brain that do not require immediate environmental inputs, including various the hard-to-define types of mental processing and sleep. I take a different approach in this book, beginning with the examination of the unperturbed, resting-sleeping brain and examining its evolving state changes. The brain's responses to environmental perturbations are addressed in later Cycles.

Rest and sleep are the best examples of self-organized operations within neuronal circuits and systems. Brain tissue can and does support spontaneous collective patterns even in the absence of any external "energizer" agent or instructions. Neurons in the thalamocortical systems can support several states, and these states follow each other according to a predictable choreography. Brain "state" is a macroscopic variable, reflected by the mean field behavior of the system, typically a characteristic oscillatory mode or a transition between different

1. Information theory quantifies the concept of information, in our case how an input signal can be reconstructed from spikes (digital output of neurons). MacKay's comprehensive book on information theory (MacKay, 2003) is available online. For the reconstruction of sensory information from spikes and a thorough quantitative treatment of the topic, see De Ruyter et al. (1997).

oscillatory modes. The state is generated by the participating neurons and defined by a set of parameters such as activation of voltage-gated channels, availability of neurotransmitters and neuromodulators, and distribution of synaptic weights. In turn, the created state variable, such as a network oscillation, constrains the firing patterns of single neurons.[2] The states change during the course of sleep, but the passage of states over time is predictable from the history of previous states.

Sleep is an excellent model of evolving brain states because it occurs without an outside influence—it evolves from within. Complex systems with a predictable "path" or trajectory in the state space are called deterministic. Sleep is such a deterministic evolving state. Unfortunately, very little is known about the mechanisms that force brain networks to change and stabilize their trajectory of activity during sleep. To date, most research on the physiology of sleep has been devoted to understanding the biophysical and pharmacological bases of the various sleep states—separately. These works have provided significant advancements in our understanding of the mechanisms involved in normal sleep and sleep alterations psychiatric disorders. Virtually every psychiatric ailment is associated with some kind of alteration of sleep duration and pattern. This change is usually interpreted as a consequence of the primary problem apparent in the waking brain. However, it is equally justified to consider causation in the opposite direction, namely, that alteration of sleep structure is the cause of the altered responsiveness of the waking brain. Deciphering the self-organized dynamics of the neuronal circuits involved in the various sleep stages and state progression may be the key to understanding the brain's responses to environmental perturbations.[3] In this Cycle, I examine sleep- and rest-associated oscillations and their mechanisms. In Cycle 8, I discuss the possible functions these oscillations may serve.

Thalamus: A Partner for Neocortex

In large systems with complex connectivity, it is often difficult to draw boundaries. This is surely the case with the neocortical mantle, with its myriads of cortical

2. Oscillations in sleep provide a striking example for "reciprocal causality." The emergent field oscillation may be considered an order parameter (collective neuronal oscillation) that constraints the timing and even the probability of neuronal action potentials.

3. The circadian and temperature rhythms are the most important "causes" of sleep. Sleep-inducing humoral factors have been suggested by several investigators. According to Borbely (1982, 1998), activity in the waking brain builds up a sleep (S) factor that is responsible for inducing sleep and delta activity. In support of his theory, sleep deprivation is followed by a homeostatic compensation (delta rebound). Rainnie et al. (1994) postulate that adenosine, acting on adenosine-1 receptors, may be such an S factor. To account for the specific and differential effects in sleep, these hypothetical factors should exert an effect locally. General, circulating factors can be largely excluded because Siamese twins with a common circulatory system sleep independently (Webb, 1978; Sackett G, Korner, 1993) and unihemispheric sleep has been documented in dolphins and other see mammals (Lyamin et al., 2002; Siegel, 2005).

modules and high-density local connectivity, supplied by neurons whose biophysical features do not vary greatly across the cortex.[4] Clustering of long-range connections already provides some anatomical clues for subdivisions of the neocortex and justifies designations of cortical systems as visual, auditory, somatosensory, motor, language-related, spatial, or other. A further segregation of neocortical function as well as integration of information across the distant regions derives from its main afferent and efferent expansion: the thalamus. This football-shaped structure is located in the origin of the two neocortical hemispheres, like the atom of a large molecule. The purpose of this geometrical arrangement—as implied in Cycle 2—could be that being equidistant from all cortical areas demands the least length of reciprocal wiring and provides the fastest axonal communication.

According to textbook wisdom, the thalamus is a large collection of relay nuclei, a kind of customs and border patrol agency. These nuclei are the only source of information for the neocortex about the body and the surrounding physical world. With the exception of olfaction, all sensory modalities are scrutinized by the thalamus before they can proceed to the neocortex. How the incoming stimuli are evaluated by the thalamus is quite a mystery, mostly because at first glance there is not too much coordination among the nuclei patrolling the different modalities. Even neighboring neurons cannot chat with each other directly, since they do not possess local axon collaterals, or only very sparse ones in some nuclei. Their axons rush up to the neocortex, terminating predominantly in layer 4 but also in layers 5 and 6; hence, they are called thalamocortical neurons.[5] Perhaps keeping sensory information segregated at this early stage is important so that the information from different sensors does not get mixed in a structure with limited capacity to extract modality-specific information. This segregation of thalamic inputs is what provides behaviorally meaningful localization of function in the neocortex.

Similar to the cortical principal cells, thalamocortical neurons release glutamate and excite their target partners. However, there are many more anatomically defined nuclei in the thalamus than there are types of sensory information. In fact, a very large part of the thalamocortical circuits do not have much to do with primary sensory information. There are important inputs from the cerebellum and the basal ganglia, but the bulk of the afferents are supplied by the neocortex. The bottom-up

4. Certain cytoarchitectural differences, e.g., the high density of layer 4 stellate neurons in the primary visual cortex or the giant Betz cells of the motor cortex in primates, do reveal boundaries, but these anatomical differences are likely the consequence rather than the cause of modality-specific segregation of function. Neocortical tissue during early development can be exchanged, and the respective tissue differentiates mainly according to its functional inputs.

5. Only a very small fraction of the excitatory neocortical synapses originates from the thalamus. Even in layer 4 neurons, the main recipients of thalamic inputs, only 5–10 percent of synapses arrive from the thalamus (Ahmed et al., 1994; Latawiec et al., 2000), and the majority of contacts originate from other cortical neurons. The number of return paths from either layer 6 or layer 5 cortical neurons to the sensory and higher order thalamic nuclei, respectively, outnumber the thalamocortical connections 5- to 10-fold (Jones, 1998, 2001)

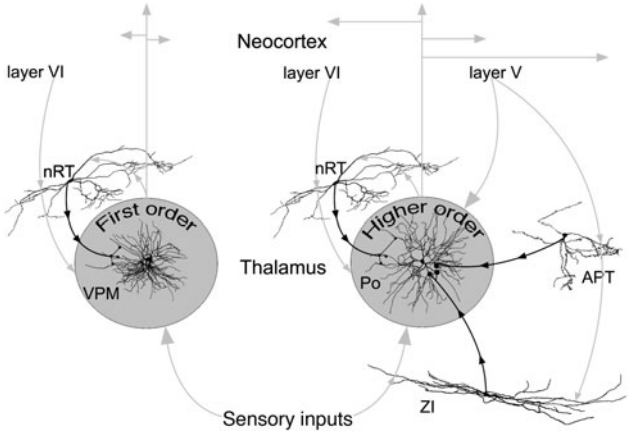

Figure 7.1. Differential neocortical and GABAergic (black lines) control of first-order and higher order thalamic nuclei. As an example, the somatosensory first-order, ventral posteromedial (VPM) nucleus, and the higher order posterior thalamic (Po) are shown. First-order nuclei are innervated by layer 6 neocortical projections and the GABAergic reticular thalamic nucleus (nRT) and give rise spatially restricted cortical projections. Higher order nuclei receive excitation from both layer 6 and layer 5. In addition to the nRT, higher order nuclei are under the inhibitory control of the zona incerta (ZI) and the anterior pretectal nucleus (APT) GABAergic system. Thalamocortical higher order neurons give rise to widespread cortical projections. Figure courtesy of László Acsády and Didier Pinault.

thalamocortical connections are reciprocated by layer 6 and also from layer 5 corticothalamic connections, according to a cleverly organized plan (figure 7.1). The importance of the cortical feedback is best illustrated by the fact that the thalamus is the only corticofugal target of the layer 6 pyramidal cell population, and these neurons innervate virtually all thalamic nuclei. In contrast, collaterals of layer 5 pyramidal cells, whose fast-conducting main axons are destined for the brainstem, target those thalamic nuclei that do not receive primary sensory or motor information. Ray Guillery at the University of Wisconsin, Madison and Murray Sherman at the State University of New York–Stony Brook call these thalamic divisions "higher order" nuclei, as opposed to the "first-order" nuclei with specific sensory-motor information. Most important, afferents from higher order nuclei send relatively widespread projections to several cortical areas; thus, they *disseminate* their information content to several other cortical regions.[6] The importance of this operation is reflected in the more extensive axon arbor commitment and larger cortical coverage of the neurons in higher order nuclei relative to their first-order partners.

6. First-order nuclei receive driving afferents from the medial lemniscus (somatosensation), the optic tract (vision), the inferior colliculus (hearing), the cerebellum (motor), and the limbic mammillary bodies. Higher order nuclei include the large pulvinar, the lateral posterior, the mediodorsal, and lateral dorsal nuclei. These novel ideas about the thalamocortical circuits are discussed at length in Sherman and Guillery (2001) and several shorter but comprehensive reviews (Guillery and Sherman, 2002; Sherman and Guillery, 2002).

The pattern of thalamic connectivity coevolved with the neocortex. However, cortical representations grew much more rapidly. For example, the number of thalamocortical neurons in the mouse is only an order of magnitude less than the number of target neurons in the cortex, whereas in the human brain the ratio is less than one to a thousand. Even though thalamic growth did not keep up with the fast development of the neocortex, higher order nuclei in primates are relatively larger than the first-order relays, indicating that allocation of divergent cortical–thalamic–cortical connections is more important for the evolution of the mammalian brain than enhancing the bandwidth capacity of primary sensory pathways. The connectivity pattern outlined above indicates that the thalamus *alone* is not a very useful structure. It does not have the ability to add or subtract information without the neocortex. However, in partnership with the neocortex, the reciprocal excitatory connections are prone to oscillation, and such a mechanism is perfectly posed to mix thalamocortical information.[7]

The cytoarchitectural organization of the thalamus is unique. Unlike in the neocortex, where inhibitory cells are nested within the excitatory networks and adjacent to their targets, most GABAergic interneurons in the thalamus reside in a thin shell surrounding the thalamic chamber, called the reticular nucleus, and some other subcortical nuclei. The evolutionary cause or advantage of the spatial segregation of inhibitory and excitatory populations is not clear. A potential advantage of placing GABAergic neurons together and far from their axonal targets is that this arrangement allows for effective local communication through, for example, electrical junctions and extensive dendrodendritic contacts. In turn, dendrodendritic junctions can release and sense locally secreted GABA, and these local mechanisms may be critical for the global operation of the reticular nucleus.[8]

On their way to the neocortex, axons of thalamocortical cells pass through the reticular nucleus, give off collaterals, and innervate the inhibitory GABAergic neurons. Interneurons of the reticular nucleus are much fewer in numbers than their thalamocortical partners; therefore, many thalamocortical cells and layer 6 cortical neurons converge onto a single reticular neuron. In turn, the reticular cells contact large numbers of thalamocortical cells. Most of them address their partners reciprocally with a high density of local axon collaterals; however, a minority have intermediate or large innervation territory capable of affecting neurons in a larger thalamic space.[9] In addition to the reticular nucleus, higher order

7. Llinás and Paré (1991) and Jones (2001).

8. Reticular thalamic neurons can communicate by three different means. In addition to traditional synaptic innervation (Scheibel and Scheibel, 1966; McCormick and Bal, 1997), they are connected by dendrodendritic synapses (Deschênes et al., 1985; Yen et al., 1985; Pineault et al., 1997; Steriade, 2001a,b, 2003) as well as gap junctions (Landisman et al., 2002). Local concentration of GABAergic neurons is not unique to the reticular nucleus. A sheet of GABAergic neurons is present between central and basolateral nuclei of the amygdala. These "intercalated" neurons are grouped together and form an anatomical and physiological barrier between the projection nuclei of the amygdala (Royer and Paré, 2003; Paré et al., 2003).

9. For a comprehensive discussion of the thalamic circuits, see Steriade et al. (1990b), Sherman and Guillery (2001), and Jones (1985). Cox et al. (1996) examined the axon arbors of single reticular

thalamic nuclei receive further inhibitory innervation from a somewhat contiguous set of structures: the zona incerta, the diencephalic anterior pretectal nucleus, and the pars reticulata division of substantia nigra. Neurons in this extrareticular inhibitory system do not receive direct thalamic information from thalamocortical neurons but receive inputs from the axon collaterals of cortical layer 5 neurons. These extrareticular inhibitory structures can be regarded as the functional boundary expansion of the thalamus.[10] Since the thalamus alone cannot generate sustained or growing excitation, due to the lack of recurrent collaterals, one may wonder why the thalamocortical neurons are under such massive inhibitory control. Information about anatomical connections alone does not provide an answer.

Single-Cell Contribution to Thalamocortical Oscillations

Per Andersen and John Eccles at the Department of Physiology, the Australian National University, Canberra noted in the early 1960s that stimulation of the neocortex or a foreleg nerve in the cat often induced initial inhibition rather than the expected excitation in thalamocortical cells, followed by a series of fast action potentials tens or hundreds of milliseconds later. They called their observation "post-anodal exaltation," referring to the requirement of an inhibition-induced hyperpolarization prior to the discharge.[11] A decade later, Rodolfo Llinás at New York University and his postdoctoral fellow Henrik Jahnsen identified the cellular mechanism of this puzzling phenomenon. At that time, most biophysicists "interrogated" neurons by injecting square-wave currents of various magnitudes into the cell bodies and evaluated the resulting membrane and spike dynamics. Llinás suspected that this approach could not be the best strategy since neurons do not communicate with square pulses. While he and Jahnsen were experimenting with various waveforms, they observed that thalamocortical cells responded in a qualitatively different manner when the same membrane potential was brought about by an arbitrary waveform from either a depolarized or a more hyperpolarized level. When synaptically excited or depolarized by an intracellular current, thalamocortical neurons behaved like "classical" neurons, emitting spike series. But the investigators were astonished

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cells, projecting to the ventrobasal nucleus in juvenile rats. Once within the nucleus, the axon ramified into one of three branching patterns: cluster, intermediate, and diffuse. The size of a cluster arborization closely approximated that of an individual barreloid with dense local branches. The intermediate structure extended across an area that was approximately fourfold greater. Neurons with diffuse arbors covered a large region of the nucleus and contained a relatively low density of axonal swellings. In contrast to the Cox et al. (1996) study, *in vivo* juxtacellular labeling of reticular neurons in the adult rat by Pineault and Deschênes (1998) revealed very few internuclear collaterals and no evidence of widespread internuclear innervation. Age difference is a potential explanation for the contrasting results.

10. László Acsády and colleagues have discovered a widespread extrareticular inhibitory system (Barthó et al., 2002; Bokor et al., 2005). These GABAergic nuclei compose a continuous system that cooperatively affects first-order and higher order nuclei of the thalamus. For the nigrothalamic and pallidothalamic connections, see Kultas-Ilinsky et al. (1983).

11. Andersen et al. (1964).

to see that thalamocortical neurons also responded when released quickly from a hyperpolarized state even without any extrinsic depolarizing force. In fact, the neurons fired a series of spikes at intervals of 3–5 milliseconds, or using the laboratory jargon, they emitted a "burst" of spikes. This was a new revelation about neurons: some neuron types, such as thalamocortical cells, can be discharged not only by excitation but also by releasing the neuron from inhibition.

The mechanism of such "rebound" excitation is the deinactivation of a Ca^{2+} channel, the T-channel, as it became known later.[12] Thus, thalamocortical cells can fire in two qualitatively different ways. Depolarization can induce rhythmic single spikes, similar to those observed in neocortical pyramidal cells. When released from hyperpolarization, activation of the T-channel leads to a "slow spike," caused by the influx of Ca^{2+} ions. Because the slow Ca^{2+} spike is depolarizing and lasts for tens of milliseconds, typically a series of fast Na^+ spikes ride on it. This discovery, in itself, is important because it illustrates a fundamentally different method of transferring information. In the "high-fidelity," Na^+-spike-only mode, sufficient excitation will briskly discharge the neuron: the stronger the depolarization, brought about by the converging excitatory inputs, the faster the thalamocortical cell's output. In the "low-fidelity," Ca^{2+}-spike mode, the effect of the input depends strongly on the state of the neuron. While the neuron discharges a burst (reflecting its duty cycle), it remains refractory to afferent activation. Following the burst, the cell gets hyperpolarized because the Ca^{2+} influx activates a hyperpolarizing K^+ channel for tens of milliseconds, making the neuron still reluctant to respond to afferent inputs. Another important consequence of this nonlinear behavior is that, when coupled with an opposing force, it provides the necessary conditions for oscillation, as the work from David McCormick of Yale University has shown. Upon hyperpolarization, another voltage-gated channel (termed I_h: also known as the pacemaker channel because it was first described in the pacemaker sinoatrial node of the heart) tends to repolarize the neuron. Adjusting the membrane potential to an appropriate hyperpolarized range by an intracellular electrode, thalamocortical neurons discharge a burst of spikes at 0.5–4 hertz, virtually infinitely (figure 7.2). Every thalamocortical neuron can therefore be converted into a delta frequency clock when properly hyperpolarized. The opposing forces required for the oscillator are the hyperpolarization-activated mixed cation (Na^+ and K^+) current, I_h, and the low-threshold Ca^{2+} current, I_T. These currents are activated at different membrane voltage levels. Hyperpolarizing the neuron beyond–65 millivolts activates I_h. The activation of I_h depolarizes the membrane slowly until a low-threshold Ca^{2+} spike is generated by activation of I_T at a more depolarized level. During the spike, I_h is deactivated, and the termination of the spike is followed by a hyperpolarizing "overshoot" that in turn begins activating I_h, and the cycle repeats. In addition to voltage, activation of I_h is also sensitive to the intracellular concentration of Ca^{2+}. The variation of intracellular Ca^{2+} can therefore adjust the "strength" of I_h, and it converts the clocklike

12. Jahnsen and Llinás (1984a,b). For reviews, see Steriade and Deschênes (1984) and Huguenard (1996).

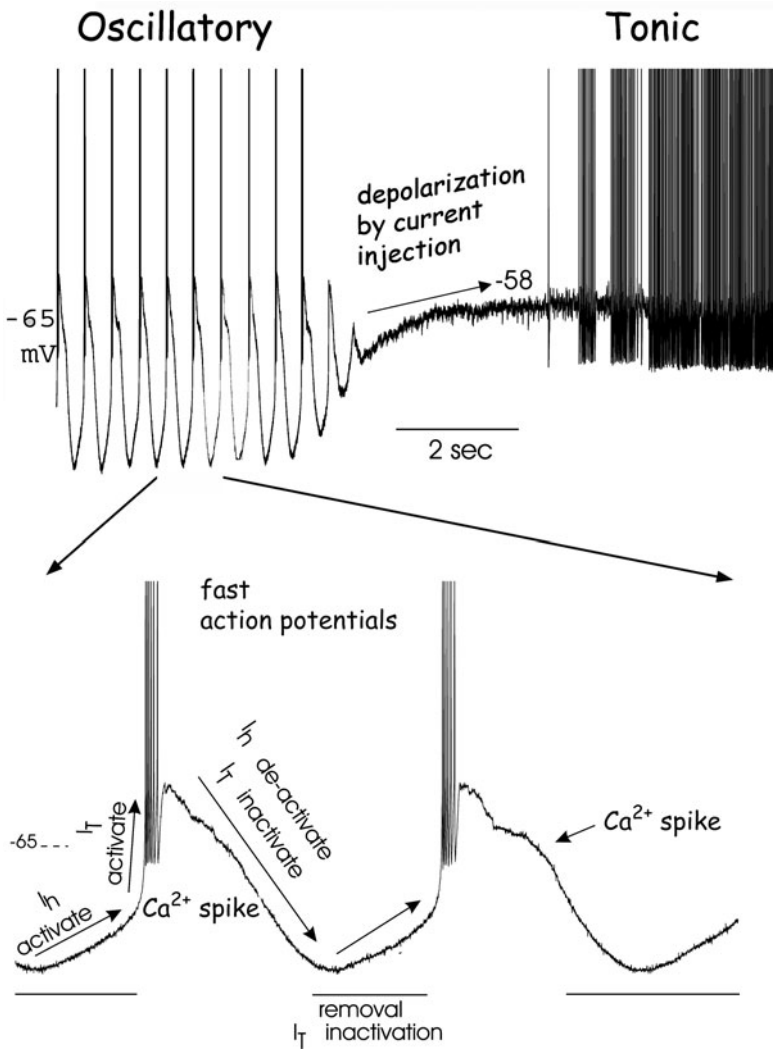

Figure 7.2. Single-cell oscillation in a thalamocortical neuron. Top: At membrane potential–65 millivolts, the neuron sustains stable oscillation at 1–2 hertz. Depolarization of the membrane induces continuous fast (Na^+) spikes. Two events are expanded in time (bottom). The hyperpolarization-activated I_h ("pacemaker") conductance repolarizes the membrane into the activation range of I_T (low-threshold Ca^{2+} channel). When I_T activates, it induces a wide Ca^{2+} spike upon which fast spikes ride. The Ca^{2+}-spike–induced depolarization deactivates I_h and inactivates I_T. The ensuing hyperpolarization initiates a new identical cycle. Reprinted, with permission, from McCormick and Pape (1990).

delta oscillation into a waxing/waning pattern, a situation more similar to the intact brain.[13]

These findings are interesting for several reasons. First, they illustrate that nature went to a lot of trouble bringing together these channels at the right densities and location just to serve one purpose: oscillation.[14] Brain evolution adopted a channel from the heart just to sustain oscillations during sleep. It is hard to imagine that such a complex and energy-expensive design is simply a byproduct. Even if bursts are also put to work for sensory transmission, their dominant occurrence during sleep is indisputable. Second, these and other oscillation-promoting channels are present in a variety of cortical neurons, although their density and spatial distribution vary substantially. Thus, in cortical neurons these channels may serve similar functions. Third, when coordinated across multiple thalamocortical neurons, the single-cell properties can provide a delta-frequency pacing of their cortical targets. Finally, inhibition-induced rebound spikes are not elicited by any specific sensory input. Because they are triggered by inhibition, in a sense, they are "useless" for the representation of upstream excitatory inputs. Rebound spike bursts therefore are the prime examples of self-generated spike patterns that communicate to downstream neurons primarily determined by the state of the thalamic network.

Reticular neurons, similar to thalamocortical cells, also contain I_T channels and therefore can generate low-threshold Ca^{2+} spikes. Although I_T channels have a slower kinetics and are activated over a more depolarized range of membrane potentials than in thalamocortical neurons,[15] isolated reticular thalamic neurons nevertheless can also sustain oscillations. Instead of I_h, however, the opposing force of I_T is a Ca^{2+}-activated K^+ current, $I_{K[Ca]}$. Although a strong hyperpolarizing pulse can also induce bursts of action potentials at delta frequency in isolated reticular neurons, the evoked oscillations quickly dampen, suggesting that reticular neurons are not critical players in delta oscillations.[16]

13. Thalamocortical neurons in the intact cat generate bursts at delta frequency (Curro Dossi et al., 1992) and become clock-like after removal of the neocortex (Timofeev et al., 2000). Similar "pacemaker oscillations" with rebound bursts at delta frequency are also present in the thalamic slice (McCormick and Pape, 1990; Leresche et al., 1990; Soltész et al., 1991) and computer models of single neurons (Toth and Crunelli, 1992; Destexhe et al., 1993; Wang, 1994; for a review, see Destexhe and Sejnowski, 2001).

14. In fact, Steriade argues that Ca^{2+} bursts in thalamocortical neurons occur exclusively during sleep. For a debate on the functional significance of "bursts," see Swadlow and Gusev (2001), Sherman (2001), and Steriade (2001c).

15. Rebound bursts in reticular neurons were first demonstrated *in vivo* (Mulle et al., 1986) and confirmed by extensive *in vitro* studies (Llinás and Geijo-Barrientos, 1988; McCormick and Wang, 1991; Huguenard and Prince, 1992).

16. The I_T-channel–mediated increase of intracellular Ca^{2+} also activates a nonspecific cation current, called I_{CAN}, which tends to depolarize the membrane. Combination of these currents in model reticular neurons produced rebound bursting at 8–11 hertz but not in the higher spindle-frequency range (Bal and McCormick, 1993; Destexhe and Sejnowski, 2001). For spindle generation, network connectivity is needed.

From Single Neurons to Network Oscillations

With the discovery of the low-threshold calcium channel and other active conductances, thinking about thalamic function has changed forever, marking the beginning of a new, very productive era of thalamic research. Research has progressed simultaneously in the intact animal and in the *in vitro* slice preparation as well as *in silico,* often with heated exchanges of ideas among the protagonists. Numerous rhythms have been described in the resting-sleeping thalamocortical system, including alpha waves (8–12 hertz), mu rhythm (8–12 hertz), sleep spindles (10–20 hertz) and associated ultrahigh-frequency oscillations (300–600 hertz), delta waves (1–4 hertz), and the slow 1 to slow 4 rhythms (0.05–1 hertz). These patterns are collectively called "thalamocortical" oscillations, indicating the involvement of both the thalamus and the cortex. However, different investigators often emphasize the primary dominance of one structure over the other for each of these patterns.

The study of thalamocortical oscillations has roughly two historical stages. During the last century, we simply observed them. Recently, we began creating them in some rudimentary but controllable and quantitative manner. Many books and reviews have dealt with these fascinating yet complicated rhythms over the years. The major debates revolve around the issue of the minimum substrate (i.e., thalamus vs. the neocortex) and mechanisms of these rhythms. A common function of all self-governed thalamocortical oscillations is that they bring about constraints regarding whether and when information about the outside world, detected by the peripheral sensors, can pass through the thalamus and be distributed for further processing in cortical networks or is ignored outright. Why are oscillations the chosen solution for the isolation of sensory inputs from the downstream cortical and other targets of the thalamus? In principle, such a "gating" function could be accomplished by tonic GABAergic inhibition without any oscillatory component. However, inhibition through the fast $GABA_A$ receptors can silence cells for only a few tens of milliseconds.[17] The inhibitory action of $GABA_B$ receptors is longer, but a much larger amount of GABA should be released for their activation, so that the transmitter molecules can passively diffuse to the receptor.[18] This is still conceivable. However, if the gating function is to be maintained at the seconds time scale, as is the case during sleep, continuous release of GABA should be secured somehow. Elevated release of GABA is possible only through the continuous excitation of the reticular thalamic and extrareticular GABAergic neurons[19] by their afferents, including subcortical neurons, sensory (lemniscal) inputs, corticothalamic

17. For a review of *in vitro* work, see Kaila (1994), Jonas et al. (2004) and Mody and Pearce (2004). In the intact brain, inhibition is even shorter than in the slice (Barthó et al., 2004).

18. For the subcellular localization of $GABA_B$ receptors, consult Somogyi et al. (1998).

19. Besides the reticular nucleus, inhibition to the thalamus is supplied by the zona incerta and pars reticulata of the substantia nigra. These GABAergic nuclei compose a continuous system that cooperatively affects first-order and higher order nuclei of the thalamus (Barthó et al., 2002; Bokor et al., 2005).

afferents, or thalamocortical cells. However, at sleep onset, subcortical neurons, releasing acetylcholine, serotonin, norepinephrine, and histamine, decrease their firing rates.[20] So do specific thalamic afferents and primary sensory cortical neurons. Thus, the expected excitatory task is left to the thalamocortical neurons, that is, to the population whose silencing is desired. Furthermore, if thalamocortical cells would discharge randomly to maintain inhibition, their non-sense activity would be heard by the neocortex, as well, potentially leading to random modification of neocortical connections.[21] As this thought experiment illustrates, silencing the principal-cell population in an interconnected system is not a simple task. Thalamocortical networks maintain activity all the time, and silence as a default is rarely chosen. Tonic or random inhibition is thus not an effective mechanism for preventing excitation unless an external control of inhibition is available. An alternative mechanism for ignoring inputs is through inhibition-based oscillations that can provide prolonged periodic suppression of activity. In the thalamocortical system, oscillations not only represent different states but also require different ionic mechanisms.

The spatial extent of cortical involvement depends primarily on the frequency of oscillations. As a rule, slower frequencies involve more extensive synchronous activation of the neuronal pool. The distribution of neuronal information across vast areas of the neocortical networks with limited interarea connections is assisted by the special wiring relationship between the GABAergic reticular cells and thalamocortical neurons, their unique biophysical properties, and the dissemination of local cortical information by the widespread higher order thalamic nuclei. In contrast to the rigid interarea corticocortical connections, with progressively increasing axon conduction delays, the transthalamic "shortcuts" are nearly equidistant from all neocortical areas.[22] With the thalamus as a matchmaker, the effective connectivity between local neocortical populations can be changed according to current computational needs. The key ingredient in this globalization process is the ability of the oscillatory mechanisms to recruit anatomically distant cortical neurons into temporal coalitions. Thus, in addition to the interarea long-range connections among the various cortical regions, the thalamus provides additional radial "shortcuts" necessary for reducing the synaptic path lengths between the various cortical areas.[23] The weak connections can be amplified by phase modulation, due to the resonant properties of the thalamic and cortical modules involved. As a result, modules with resonant relations between

20. Foote et al. (1983) and Steriade and Buzsáki (1990).

21. Thalamus-mediated sensory inputs are believed to play a critical role in the fine tuning of cortical circuits (Katz and Shatz, 1996). According to such a postulated mechanism, random discharge of thalamic neurons would randomize cortical connections.

22. A good example is the pulvinar, which is an "associative" visual thalamic nucleus. The pulvinar contains blurred maps of visual cortical areas V1–V5, in addition to other cortical projections. As a result, the indirect cortical–pulvinar–cortical circuits tend to mimic direct corticocortical pathways but with more extensive overlap. These widespread projections allow the pulvinar to coordinate cortical information processing by facilitating and sustaining the formation of synchronized transarea assemblies and outlasting each other in activity (Shipp, 2003).

their frequencies can exchange information more easily than modules with nonoscillating properties or dissimilar frequencies.[24]

Viewed from this new anatomical-physiological perspective, the thalamus is no longer a gigantic array of independent relays but a large communication hub that assists in linking large cortical areas in a flexible manner. The principal mechanism of the cortical–thalamic–cortical flow of activity is self-sustained oscillations.

Oscillatory Patterns of Sleep

Unlike most body parts, the brain is busy at night, as well. A main function of sleep is to isolate the brain from the body and the environment, which is the reason why we can call it a default state. When all subcortical inputs to the thalamus are severed by a horizontal cut through the brainstem of a cat between the superior and inferior colliculi, the neocortex displays waxing and waning oscillatory patterns at 10–20 per second alternating with relatively flat, low-voltage EEG. Because in this highly transected brain, or *cerveau isolé,* preparation, as Frederic Bremer at L'école de Médecine de l'Université Libre de Bruxelles called it, the pupils of the cat are constricted and because similar spindles are also observed in superficial stages of sleep (see below), Bremer concluded that this deafferented brain is in constant sleep.[25] On the other hand, if the cut is made in the midpontine region, preserving the mesencephalon's key structures (e.g., the noradrenergic locus ceruleus and the cholinergic pedunculopontine/laterodorsal tegmental nuclei), the cat is awake most of the time with dilated pupils and is able to track visual stimuli.[26] In a different, so-called *encéphale isolé,* preparation, the

23. Speed limitations should be kept in mind, however. Layer 6 corticothalamic fibers are very thin, and it may take 20–40 milliseconds for an action potential to reach the thalamic terminals. Layer 5 projections to higher order thalamic nuclei have much faster conduction velocities, however (Swadlow, 2000). Miller (1996a, b) suggested that the cortical–thalamic–cortical loops tie together cell assemblies whose neuron members are dispersed throughout the neocortex.

24. Hoppenstead and Izhikevich (1998) use the analogy of radio frequency modulation (FM): the frequency of oscillation encodes the radio station, while the information is transmitted via phase modulations.

25. Bremer (1935). Prior to these early works, sleep was thought to be a passive process. Purkinje (1846) speculated that sleep was caused by a functional interruption of connections between the brainstem and the forebrain. This view was amplified by Constantin von Economo's famous observation that the likely cause of the pronounced somnolence (lethargy) in patients with "encephalitis lethargica" (sleeping sickness) was extensive damage to their brainstem (von Economo, 1928). Because this sleeping sickness reached epidemic proportions during and after World War I, it was believed to be mediated by a virus, although an etiological agent was never identified. Steriade (2001b) is an excellent source of information on these early experiments, along with the discovery and impact of the reticular activating system described in Moruzzi and Magoun (1949).

26. Batini (1959). During wake/sleep transition, not only are the sensory inputs decreased but also many other mechanisms, including decreased release of subcortical neuromodulators, are in action (Steriade, 2001a). The various neuromodulators of the brainstem affect mostly the slow K^+ channels in their target cells and effectively "scramble" their spike times (Steriade and Buzsáki, 1990).

transection is performed at the caudal end of the medulla, just above the spinal cord. The *encéphale isolé* cat shows normal sleep/wake cycles. The major conclusion of these and many subsequent experiments is that it is the subcortical neuromodulators that keep the thalamocortical system awake rather than sensory stimuli from the body and the environment. Furthermore, the thalamocortical system alone cannot show organized sequences of sleep stages but is trapped in a single superficial sleep stage.

Because sleep is not simply a suspension of waking activities, there must be a good reason why complex brains have developed an elaborate choreography of sleep. In humans, at least five stages with progressively higher wakening threshold can be distinguished, with the deepest stage being the rapid eye movement (REM) phase (figure 7.3). Separation of the first four stages, known collectively as "non-REM" sleep, is based mostly on the relative numbers of sleep spindles and delta waves observed (discussed below). Stage 1 is the phase transition between wake and sleep. It consists of a relatively low-voltage EEG with mixed frequencies, mainly slow alpha and theta activity. Stage 2 is heralded by the emergence of sleep spindles and K-complexes. Stage 3 is a mixture of spindles and delta waves (20–50 percent), whereas stage 4 is characterized by the dominance of delta activity with only traces of spindles. Approximately half of sleep consist of stages 2 and 3; stage 4 composes only 5–15 percent of total sleep time and may be completely missing after 40 years of age. Stages 3 and 4 are often referred to as slow-wave or delta sleep. Although stage classification of sleep is useful for pragmatic and clinical purposes, the temporal boundaries of these stages are not precise. The electrical patterns of the fifth stage, REM sleep, are characterized by waking-type scalp EEG, rapid eye movements, loss of muscle tone, and dreaming. REM sleep composes usually 20–25 percent of total sleep time in human adults, and it is an indication of the end of a non-REM/REM sleep cycle.

Typically, four or five non-REM/REM cycles with a period of 70–90 minutes each occur within a night. These five stages are organized into a periodic sequence, giving a dampened oscillator appearance to the macrostructure of sleep (figure 7.3).[27] The evolving patterns are characterized by various oscillations at different frequencies with different degrees of involvement of the various cortical and thalamic structures. Ultradian periodicity is not unique to sleep but is also reflected by the oscillatory nature of vigilance levels and cognitive performance throughout the day.[28] In other words, in the absence of environmental inputs or an explicit algorithm, the brain gives rise to self-organized activity that follows a complex trajectory in time and neuronal space.

As discussed in Cycle 5, the 1/*f* nature of brain signals reflects their history dependence, a result of lumping long epochs. However, this long-term picture of high

27. The dampened oscillatory pattern of sleep varies during ontogeny and is perturbed in many psychiatric illnesses.

28. Principal component analysis of subjective sleepiness and objective spectral analysis of daytime EEG showed correlated features of ultradian rhythmicities, with periods of about 100 min and 3–8 hours, with highest sleepiness index early in mid-afternoon (Tsuji and Kobayashi, 1988).

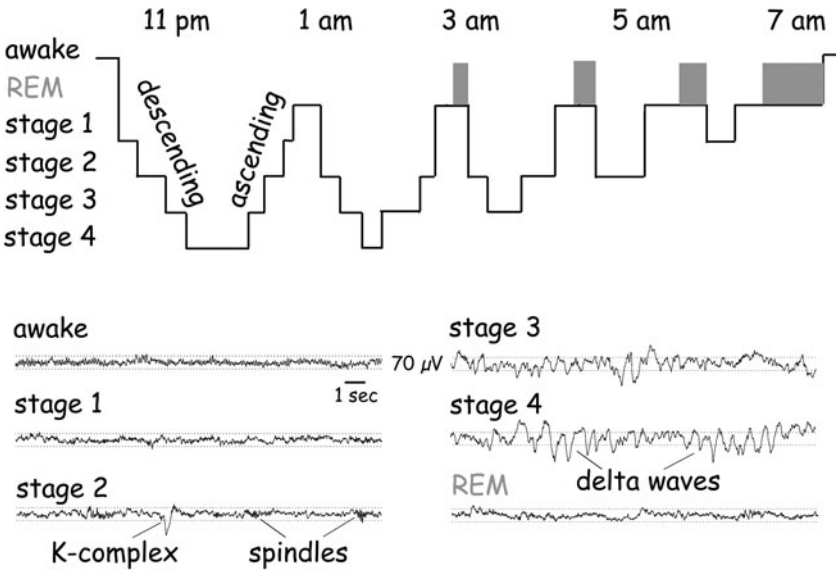

Figure 7.3. Sleep is a dampened oscillation with approximately 90-minute periods. Top: Hypnogram of a night's sleep in a young adult human. Note periodic ascending and descending phases. Bottom: Representative scalp-recorded EEG segments from each sleep stage. EEG traces are courtesy of A.A. Borbely.

dimensionality and high entropy is very different if shorter time slices are examined, because transient oscillatory couplings reduce dimensionality and increase order. Each evolving sleep stage has it own characteristic oscillatory pattern. This is not surprising, based on what we have learned about the requirements of oscillators. Oscillation is the inherent global behavior of balanced systems, whose frequency is determined by some time constants of its constituents, such as intrinsic properties or synaptic and axon conduction delays of neurons in the case of the brain. In the thalamocortical system, numerous time constants arise from the intrinsic properties of neurons, axon conduction, and synaptic delays, providing multiple possibilities for both oscillation frequency ranges and spatial extent of neuronal involvement. Below, I briefly overview the characteristic physiological patterns of sleep.

Sleep Spindles

Sleep spindles are the hallmark of natural non-REM sleep. After their sporadic onset following the slow alpha dominance, the intensity of sleep spindles increases progressively. With the increasing enslavement to oscillations, the responsiveness of neurons to other sensory and motor perturbations decreases further as sleep deepens.

A key element for the generation of sleep spindles is the mutual interaction between the GABAergic reticular neurons and the excitatory thalamocortical cells. Let us assume that a small group of thalamocortical neurons, which jointly

innervate one or more reticular neurons, discharge together by chance, similar to the emergence of hand clapping after a theater performance. All that is needed for the emergence of oscillation is a seed of enough synchrony so that some reticular neurons discharge, preferably a synchronous burst of spikes. The discharging reticular cells now hyperpolarize the same and more thalamocortical neurons because their axon collaterals diverge onto many thalamocortical neurons. The next key event is that the inhibitory currents will bring the membrane of the thalamocortical cells into the active range of I_h, and I_h, in turn, will depolarize the membrane, activate I_T, and produce a burst of spikes both in those neurons that initiated the events in the first place and in other neurons. Because the rebound spikes in the hyperpolarized thalamocortical neurons occur in synchrony, they can initiate a new cycle and recruit more neurons in the next cycles by the same mechanism as in the first.[29] In support of this hypothetical scenario, McCormick and colleagues found that a burst of action potentials in a single reticular neuron could generate an inhibitory postsynaptic potential in thalamocortical cells that was large enough to result in the occurrence of a rebound low-threshold Ca^{2+} spike and a burst of action potentials. Some of the bursting thalamocortical cells, in turn, resulted in the generation of a "return" or "feedback" barrage of excitatory postsynaptic potentials in the originating single reticular neuron. This simple, disynaptic loop is proposed to be the basis for the generation of spindle waves.

Even if this simple model can account for the emergence of spindles on the basis of known connectivity and single neuron biophysics, it falls short in explaining several other features of thalamocortical spindles. First, spontaneous "seeds" of synchrony can occur at several thalamic spots relatively simultaneously. With local thalamic connectivity only, it is hard to see how these seeds of spindles can become synchronized. Indeed, both *in vitro* slice work and computation models

29. Because lesions of the reticular nucleus, but not the neocortex (Morison and Basset, 1945), abolish spindles (Steriade et al., 1995) and because barbiturate-induced oscillations survive in the isolated reticular thalamic tissue (Steriade et al., 1990a,b), Steriade and colleagues suggested that the reticular thalamus alone acts as a true pacemaker (Steriade et al., 1990b; 1993c). As discussed above, reticular neurons can communicate with each other by synaptically released GABA, dendrodendritic synapses, and gap junctions. In principle, such connectivity may be sufficient for a pacemaker substrate. Nevertheless, because blockade of *N*-methyl-D-asparate (NMDA) receptors in the thalamus, that interfered with the slow excitatory transmission, abolished oscillations in the cortex of the rat, I suggested that the minimum circuit for spindles involves both reticular and thalamocortical neurons (Buzsáki,et al., 1990). This model is essentially an update of the thalamocortical–local interneuron circuit of Andersen and Andersson (1968), but the local interneuron is replaced by the reticular cells (Scheibel and Scheibel, 1966). *In vitro* work and computational models support the partnership model (Steriade et al., 1993c; Destexhe et al. 1994; McCormick and Bal, 1997; Destexhe and Sejnowski, 2001). The most direct evidence for the model, using dual intracellular recordings, was obtained from slices of the geniculate body of the ferret (Kim et al., 1997). It should be noted, however, that sleep spindles are rare in the occipital cortical region; therefore, it is surprising to see a spindle-generating mechanism in its thalamic input. Because the frequency of the oscillation in the geniculate slice is typically in the range of the alpha frequency band, it may well be that the oscillation described in the lateral geniculate body is, in fact, more relevant to alpha oscillations than to sleep spindles.

demonstrate that with local connections only, spindles emerge at almost any arbitrary location and travel at the speed of approximately 0.5 millimeter per second. In contrast, spindles in the thalamus of the intact brain occur synchronously, which explains why cortically recorded spindles are also coherent over a relatively large area. The cortical mechanism of this global synchrony was demonstrated in an elegant experiment by Mircea Steriade and his colleagues at Laval University, Quebec, Canada. First, they showed synchronous barbiturate-induced spindles in the thalamus of the intact cat over several millimeters. In the second part of the experiment, they removed the entire cortical hemisphere. This procedure did not prevent the continued occurrence of thalamic spindles. However, the spindles were no longer synchronized but behaved like spindles in the isolated *in vitro* thalamic slice preparation; that is, spindles from several site emerged independently and asynchronously. If a traveling spindle wave emerging from one site collided with another, the collision prevented further propagation.

The second problem with the two-neuron partnership model is that a single pacemaker cannot account for the observation that, in both humans and other animals, the frequency of frontally recorded spindles is slower (about 12 per second) than that of spindles above the centroparietal cortex (about 14 per second).[30] These differences in synchrony further support the notion that several seeds of synchrony can emerge within the thalamus that are temporally coordinated by their corresponding neocortical networks (figure 7.4).[31]

Slow 1 Oscillation

In the August 1993 issue of the *Journal of Neuroscience,* three papers appeared back to back on the same topic. In them, Steriade and his collaborators described a novel cortical oscillatory pattern. They broke away from the traditional Greek lettering tradition of frequency band labels and referred to the novel rhythm simply

30. Gibbs and Gibbs (1950) and Jankel and Niedermeyer (1985). The two types of spindle activity show different maturational courses. The power of frontal spindles is greatest in young children (up to about 5 years old) and rapidly decreases across the first decade of life; by contrast, the spectral power of centroparietal spindles varies little across age (Shinomiya et al., 1999). For a recent review on sleep spindles, see De Gennaro and Ferrara (2003).

31. Not all thalamic neurons are innervated by the reticular group. Thalamocortical neurons in the anteroventral and anteromedial nuclei do not discharge coherently with other thalamocortical neurons during barbiturate-induced spindles or in the *cerveau isolé* cat preparation (Paré et al., 1987). These nuclei, together with the neurons of the mediodorsal nucleus of the thalamus, connect limbic system structures, e.g., the amygdala, with the prefrontal, cingulate, and temporal cortices. Instead of innervation from the reticular nucleus, these limbic-system–associated thalamic neurons may receive their GABAergic innervation and rhythm from the zona incerta or other inputs (Barthó et al., 2002; Bokor et al., 2005). This difference in inhibitory control could explain the existence of two families of sleep oscillations, a slower (8–12 hertz) frontal and a faster (12–20 hertz) more posterior rhythm (Ueda et al., 2001). For traveling spindles *in vitro,* see Kim et al. (1997), and for computer models, consult Destexhe and Sejnowski (2001). The effects of decortication on the synchrony of thalamic spindles are described in Contreras et al. (1996, 1997). Long-range horizontal connections are absent in the newborn rat. As predicted from the lesion experiments in adult rats, cortical spindles remain localized or travel slowly in the newborn (Khazipov et al., 2004). For a large-scale and detailed computational modeling of sleep spindles and other thalamocortical rhythms, see Traub et al. (2002).

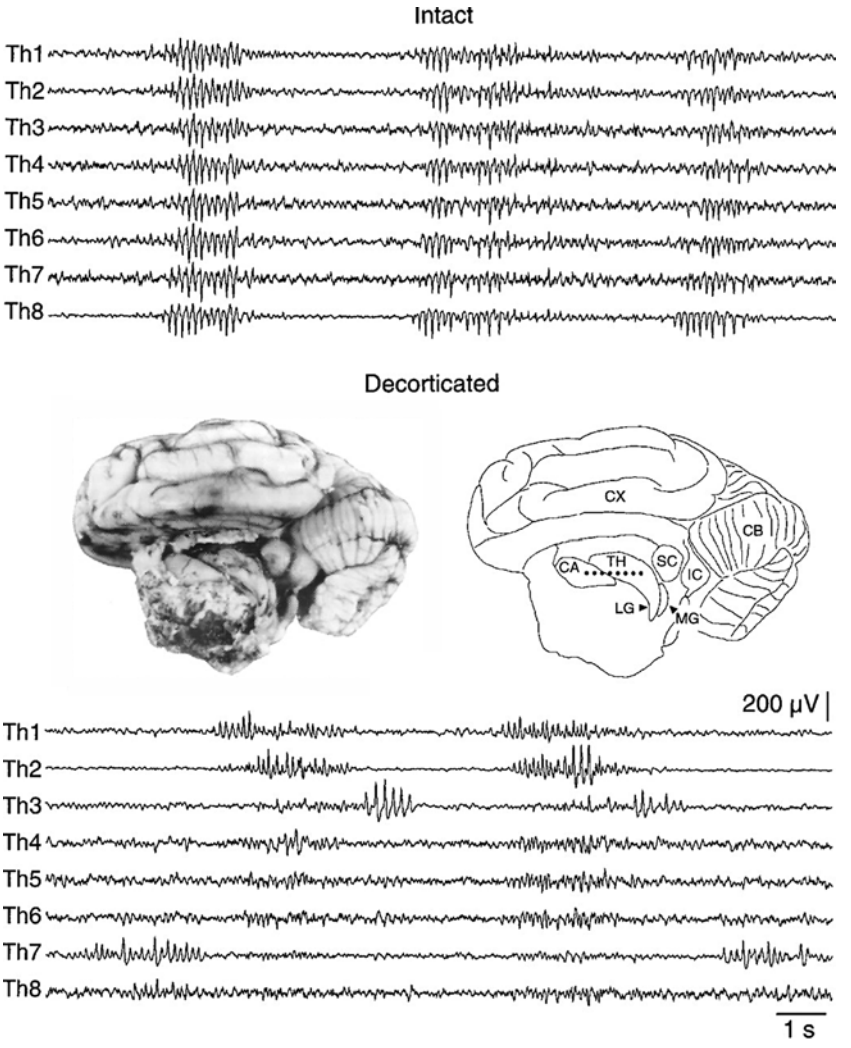

Figure 7.4. Cortical long-range connections synchronize thalamic activity. Top: Barbiturate-induced spindles (8–9 hertz, lasting for 1–3 seconds) are synchronous at multiple site in the thalamus (black dots in inset indicate recording sites Th1–Th8). Bottom: Following decortication, spindling continued to occur at each electrode site, but their temporal synchrony was disrupted. Reprinted, with permission, from Contreras et al. (1996).

as "slow" oscillation because its frequency was less than 1 per second (referred to as slow 1 in Cycle 5). Despite its modest name, the new pattern catapulted to fame instantaneously. The slow 1 oscillation was soon found also in the human EEG during sleep and was reproduced in cortical slice preparations *in vitro.*

Perhaps the most important feature of the slow 1 oscillation is its association

with a steplike change in the membrane potential of neocortical pyramidal neurons from–70 to–80 millivolts to spike threshold. The hyperpolarized "down" state is not simply due to synaptic inhibition. The neuron can be in the down state for several seconds, much longer than expected by GABA-receptor–mediated inhibition or spike afterhyperpolarization. Indeed, the membrane voltage in the down state is virtually flat (figure 7.5), indicating the lack or extreme paucity of synaptic activity. This finding is further supported by the increased input resistance of the neuron in the down state and by the observation that nearby and distant neurons change their states synchronously. In large areas of the neocortex, entorhinal cortex, subiculum, thalamus, and striatum, most neurons are either simultaneously hyperpolarized or stay in their "up" state, close to spike threshold. The hyperpolarized down state, therefore, reflects mostly withdrawal of synaptic barrages, since nearly all neurons are silent. The up state may emerge as a consequence of excitation through reentrant loops of layer 5 pyramidal neurons and is characterized by self-sustained depolarizing activity in both deep and more superficial cortical layers. The dynamics of the up and down state transitions have not been studied in great detail yet.[32] In several respects, the bistable behavior of the membrane is reminiscent of the open/closed states of membrane channels but on a larger scale. Both events may be stochastic or governed by a power law.[33]

Although it is the coherent changes of the polarization states of many neurons that give rise to the slow rhythm in the extracellular space, the up and down shift and the slow 1 oscillation can be dissociated. For example, under deep anesthesia, several seconds of silence are followed by a few seconds of the up state. Small cortical slabs, isolated by undercutting subcortical inputs and severing long-range connections, also sustain up and down shifts. However, the short, 1- to 2-second up states are separated by total silence lasting up to a minute. Up-down transitions can also be replicated in cortical slices, indicating that the intracortical connectivity is the minimum and perhaps sufficient condition for their occurrence. However, in the *in vitro* slice preparation, 1- to 3-second-long up state events are interrupted by 5–10 seconds of silence.[34]

The fast transition from silence to population activity is reminiscent of self-organized criticality, in which nonlinear interactions among the constituents evolve into a critical state over time without an external agent. On the other hand, external perturbations can also shift the complex system into a critical state. For example, electrical stimulation in the down state can induce an up state shift, provided

32. The down state is caused by K^+ channel activation and not by GABAergic inhibition (Kaila et al, 1993). McCormick and colleagues have studied extensively the self-organizing properties of the up and down states in cortical slices (Sanchez-Vives and McCormick, 2000; Shu et al., 2003b).

33. The latter possibility is indicated by the power-law scaling behavior of EEG and MEG in the 10–20 per second frequency band (Linkenkaer-Hansen et al., 2001) because sleep spindles are coupled to the up state shift (Steriade et al., 1993b).

34. The fact that a completely silent cortical network can spontaneously revert back to activity is further support for the notion that the default state of neurons is spiking rather than silence.

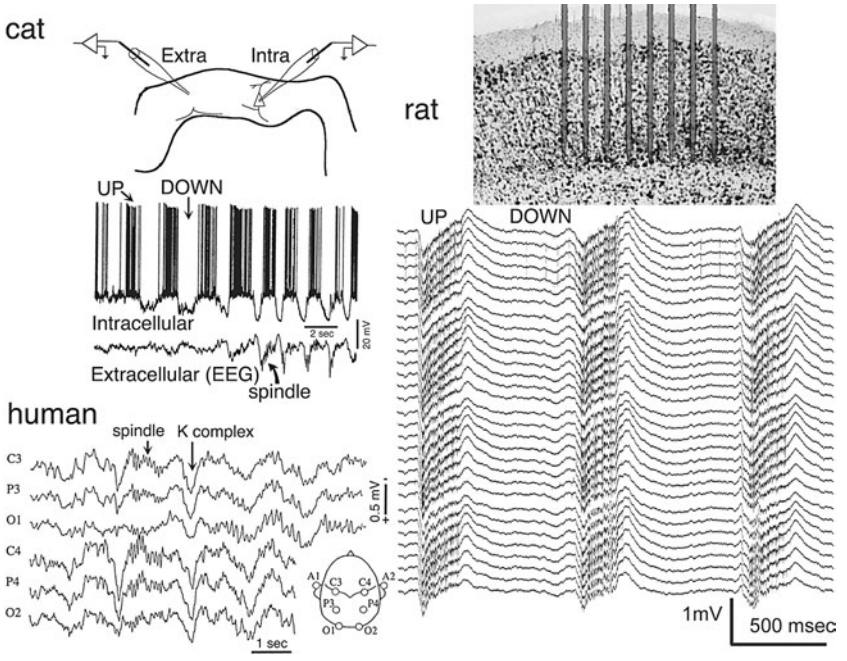

Figure 7.5. Cortical slow oscillation can trigger thalamocortical sleep spindles. Top left: Intracellular and extracellular recordings of a cat under urethane anesthesia. Note sudden and rhythmic changes of the membrane potentials between hyperpolarized (down) and depolarized (up) states and correlated EEG waves. The down-up shift can trigger spindle oscillations (spindle). Reprinted, with permission, from Steriade et al. (1993d). Bottom left: In scalp recording of EEG in humans, the down-up shifts produce a sharp potential, known as the K-complex in non-REM sleep. Reprinted, with permission, from Amzica and Steriade (1997). Right: Large-scale recordings in the rat with multiple silicon probes from the somatosensory cortex show virtually no spiking activity during the down state. Reprinted, with permission, from Barthó et al. (2004).

that the stimulus is applied after some minimum refractory period. The same exact stimulus can terminate the up state. These *in vitro* stimulation studies provide some insight into the mechanism of bistability in neocortical networks. Stimulation during the silent period induces slightly stronger excitation than inhibition. This perturbation brings about a balanced pattern of excitation and inhibition in the recurrent cortical networks, which sustains activity for a while. Once the network is active, the same stimulus evokes stronger inhibition and abruptly terminates the up state, if applied around the time when the up state is about to terminate spontaneously. This is interesting because the *same* cortical inputs can produce a diametrically opposite change in the network state, depending on the short-term history of the network.

The mechanisms responsible for bringing the active network back to silence are not well understood. A combination of various factors, including decreasing

input resistance of neurons, activity-dependent K^+ currents, and gain of inhibition over excitation, are considered opposing forces of excitation that collectively revert the network into a silent state. Anesthetics that increase K^+ conductance or potentiate the action of GABA can prolong the down state. In contrast, cortical neurons in the waking brain stay virtually constantly in the upstate. A major reason for this is that a main action of subcortical neurotransmitters is to decrease K^+ conductance of cortical neurons.

Recurrent and lateral excitation is the main mechanism through which excitation can spread. This process takes time, given the low velocity of axon conductance. By stimulating the network and recording activity at various distances, one can see how the latency of the up shift grows progressively longer with neurons farther from the stimulation electrode. Spontaneous events also spread as a wave. The seed of excitation in the cortical slice is not necessarily fixed and can vary from one event to the next.[35] Studies on humans also document the traveling wave nature of slow oscillation. Each wave originates at a definite location and sweeps small or large parts of the cerebral cortex at a speed of 1–7 millimeters per millisecond. This is about 10 times faster than in the isolated cortical slab of the anesthetized cat or in the cortical slice preparation of the rat and may be due to the presence of intermediate- and long-range connections in the intact brain.[36]

The participation of neurons in successive up and down events is not random. In the intact rat brain, the same set of neurons tends to initiate the up shift, and the recruitment of subsequent neurons is also quite similar in subsequent events. It is not clear what makes some neurons initiators and others followers, but it is likely that synaptic connectivity plays an important role. Neurons that are more strongly connected are more prone to be part of the initial event than neurons with weaker synaptic links. One can only speculate that the synaptic weights that determine the propagation direction of excitation were brought about by experience in the waking state. This hypothesis would explain why anesthesia does not erase memories prior to the induction of anesthesia. If neurons fired randomly under the influence of anesthetics, such activity might equalize synaptic weights, potentially leading to the erasure of previously learned skills and experiences.

The slow 1 oscillation does what it is expected to do: it biases the occurrence of non-REM sleep–associated patterns, including gamma oscillation and sleep spindles. In addition, the slow oscillation can explain two more clinically well-known patterns of slow-wave sleep: delta waves and K-complexes.

35. Steriade et al. (1993b,d,e), Timofeev et al. (2000) described slow oscillations in the isolated cortical slab. For a review on slow oscillations, see Steriade (2001a, b; 2003). For possible mechanisms of slow oscillations, see Sanchez-Vives and McCormick (2000), Compte et al. (2003), Shu et al. (2003a,b), Petersen et al. (2003) and Petersen (2003). Achermann and Borbely (1997) identified slow oscillations in the human sleep EEG.

36. Massimini et al. (2004) described the traveling wave nature of the slow oscillation and provided several other quantitative accounts of the propagation. The cellular events underlying the directed nature of the traveling wave may be important for spike-timing–dependent plasticity (Ermentrout and Kleinfeld, 2001).

Origin of Delta Waves

As discussed above, the duration of both up and down states can be quite long under anesthesia and especially in the isolated cortical slab, in which the duration of neuronal silence can be maintained for tens of seconds. Such long silent (down) episodes are never observed in the intact, drug-free brain. The longest silent periods last for 100–500 milliseconds during stage 3 and 4 sleep, associated with a surface negative slow pattern, known as the delta wave. Similar to the down state of the slow 1 oscillation, delta waves occur synchronously over the entire neocortex. We can conclude, therefore, that delta waves of slow-wave sleep correspond to the transient down state of the slow 1 oscillation. Although nearly all principal neurons in all neocortical layers become silent relatively simultaneously, the large cell bodies of layer 5 neurons generate most of the measurable extracellular currents. The hyperpolarizing shift in the cell bodies is reflected as a positive wave in deep layers and draws current from the superficial layers where delta waves have a negative polarity. This novel interpretation of delta waves is in line with previous knowledge about delta sleep patterns. During delta oscillations, the deep positive waves are associated with an increase in K^+ conductance and increased input resistance of single neurons, which can be readily abolished by the activating neurotransmitters acetylcholine or norepinephrine.[37] As discussed above, in deeper stages of sleep, thalamocortical neurons can sustain oscillations in the delta frequency band (1–4 hertz). At the same time, the neocortex displays groups of delta waves with a periodicity in the same range. One potential mechanism of such a grouping is that the thalamic output toggles the neocortex back and forth between up and down states. The initiator of this flip-flop event is not known and probably involves several mechanisms. One source is neocortical, since down-up shifts can occur in the absence of the thalamus, whereas the thalamocortical cells without the cortex show nonsynchronous delta frequency oscillations.[38]

37. Steriade et al. (1993b,d,e) have already noted that down-up shifts of the slow oscillation triggered sleep spindles. The association between sleep spindles and slow oscillation in humans was demonstrated by Mölle et al. (2002). Buzsáki et al. (1988) showed that delta waves are not due to inhibitory postsynaptic potentials, and Metherate and Ashe (1993) found that delta waves were associated with a K^+ conductance increase. Both studies implied that a main role of the cholinergic basal forebrain is to block the K^+ conductance (delta activity), which action is interpreted as "cortical arousal." For a review of the relationship between behavioral and electrophysiological arousal, see Steriade and Buzsáki (1990), and for the cholinergic blockade of the down state, see Steriade et al. (1993a).

38. All neuron types of the thalamocortical partnership participate in large-scale oscillations of alpha, spindle, delta, and even slow 1 oscillations, although different factors may dominate each of these patterns. The involvement of voltage-gated channels can explain the competition between spindle oscillations and slower patterns, since the membrane can be only at one voltage level at a time. During sleep spindles the membrane potentials of thalamocortical neurons are between –55 and –65 millivolts, whereas delta oscillations occur in the range –68 and –90 millivolts. The progressive hyperpolarization of thalamocortical neurons during the course of sleep may explain the prevalence of spindles in early stages and delta dominance in stage 4 sleep (Nuñez et al., 1992). A portion of reticular neurons also displays up and down states (Fuentealba et al., 2005).

The reciprocally connected toggle switches, the cortex and thalamic circuits, can easily bias each other's bistable states. A synchronous discharge of cortical neurons during the upswing of the membrane can cause an up state shift in the reticular neurons; in this state, they become more sensitive to other excitatory inputs, for example, to volleys from the thalamocortical cells. The synchronized volleys of the thalamocortical neurons can also alter the state of cortical neurons, depending on their membrane potential. From this perspective, the occasional delta rhythm in stage 4 sleep is a special temporal case of the up-down shifts of cortical activity, reflecting relatively symmetrical up and down states, corresponding to the duration of delta waves. A critical part of this process is the sufficiently hyperpolarized state of thalamocortical neurons and the associated transient silence of neuronal activity in large areas of the neocortex, reflected in the EEG as a spatially coherent delta wave.[39]

Down-Up Shifts Trigger K-Complexes and Sleep Spindles

It has been known for many decades that spindles are often preceded by a large-amplitude wave with a sharp component, reminiscent of the shape of the letter K, for which reason they are called K-complexes. This distinctive EEG pattern occurs most frequently during stages 2 and 3 of sleep, that is, when the occurrence of sleep spindles is also highest. The field potential K-complex is associated with a population burst discharge of cortical neurons, including layer 5 and 6 pyramidal cells projecting to the thalamus. Such a strong and synchronous input may discharge reticular cells directly or indirectly and thus could serve as the initiator of sleep spindles. But how do K-complexes emerge? In more superficial sleep states, K-complexes can be elicited by all modalities of sensory stimuli, including slight positional changes in bed. The multimodality of sensory inputs can explain the spatial variability of the slow-wave/K-complex initiation in different cortical sites. For these reasons, it has been debated whether K-complexes reflect transient cortical arousal or sleep-protective events.[40] It is possible that the frequent association of spindles with K-complexes serves to disengage the cortex from the sensory input by the self-organized spindle mechanisms.

An endogenous trigger for sleep spindles is the down-up shifts of the slow 1 oscillation. These shifts are associated with a widespread and strongly synchronous discharge of cortical principal cells. In the extracellular field, the rapid down-up transition in a large number of neurons results in a complex waveform, the "spontaneous" K-complex (figure 7.5). If the fast recruitment of cortical neurons during the down-up shift occurs at times when thalamocortical neurons are in the activation

39. Recently, a slow rhythmic modulation of delta power has been described in human sleep. This ultraslow oscillation of power with a mean period of approximately 15 minutes appears to be an integral characteristic of the early non-REM sleep (Merica and Fortune, 2000).

40. Loomis et al. (1938), Roth et al. (1956), Halász et al. (1985), and Bastien and Campbell (1992). For a recent review on K-complexes, see Halász et al. (2004). For the physiological correlates of K-complexes, see Amzica and Steriade (1997, 1998).

range of I_h and I_T, a spindle is initiated. In humans, this relationship is reflected by the strong correlation between slow 1 oscillation and the occurrence of sleep spindles. If the up shift can bring about strong enough depolarization in cortical neurons, transient gamma-frequency oscillation may be elicited instead of a spindle. Such transient gamma rhythms during sleep may justify the clinically used term "microarousal."

Descending and Ascending Phases of Sleep Cycles

Over the past few decades, we have witnessed a spectacular progress in our understanding of the mechanisms of the various sleep oscillations. Yet, we have learned very little about the interactions of these oscillations and the mechanisms that bring about transition between the various sleep stages. Once the brain spends enough time in stage 4 sleep with large delta oscillations, it descends from this highly perturbation-resistant condition to more shallow states. In stage 2 of the ascending phase, the thalamocortical system arrives at an important bifurcation point, a choice between awakening and REM sleep. The periods of the descending and ascending phases of subsequent sleep cycles are quite similar but their depth of modulation progressively diminishes during the night (figure 7.3). At the top of every ascending phase, the brain faces the same bifurcation problem: to wake up and be in control of the body or loose control of the skeletal musculature and fall into REM sleep.[41] Yet, during the first four cycles, the choice is typically REM; the path of continuous waking is chosen only after the fifth or sixth cycle.[42] All these transitions and stabilization of sleep stages evolve without a supervisor or external influences.[43]

The forebrain EEG and many other physiological parameters of REM sleep are quite similar to the waking state. However, the ability of sensory inputs to perturb the brain reaches its minimum, and the nearly complete loss of muscle tone paralyzes the body, preventing it from responding to the environment. The

41. The brain still is in charge of important vegetative functions, e.g., heart rate, blood pressure, temperature, respiration, bowel movement, and blood sugar. Furthermore, communication between the brain and body also includes hormonal signaling that continues to be active in all stages of sleep (e.g., McEwen and Lasley, 2002).

42. Born et al. (1999). The "choice" between waking and REM sleep at the peak of the ascending phase is perhaps the most intriguing point in the sleep cycle because it is the choice of simultaneously enhancing or blocking the sensory inputs and motor outputs. REM sleep is the ultimate environment- and body-deprived activity of the brain.

43. Day/night changes may be viewed as external influences, which are known to affect sleep, perhaps through the circadian oscillator. Human volunteers isolated from such external phase-resetting events can develop prolonged sleep cycles alternating with proportionally extended waking periods (Strogatz et al., 1986). The orderly regulated sleep patterns in the normal brain are substantially altered in numerous psychiatric diseases. It is tacitly assumed that sleep disturbance is a consequence of the daily environmental interactions. One may wonder, however, whether the primary perturbation is to be sought in the self-organizing ability of the brain, as reflected by sleep patterns, and whether the disease is a consequence of the altered patterns of sleep. Sleep deprivation is known to induce hallucinations, acute paranoia, and other symptoms (Babkoff et al., 1989), supporting such a conjecture.

discrepancy between forebrain physiological parameters and the state of the skeletal muscle system led the French sleep research pioneer Michel Jouvet to call this state "paradoxical."[44]

Given the deterministic nature of sleep, the initial conditions, that is, the state of the brain network modified by the daytime experience, should predict the order parameters and neuronal content of sleep.[45] These fascinating issues are discussed in Cycle 8.

Partial Disengagement from the Environment: Family of Alpha Rhythms

Sleep is a drastic and global isolation of the cerebral cortex from environmental inputs. What if we just eliminate one input at a time? This is as easy as shutting your eyes. Once the eyelids are closed, the eyeball ceases its routine of slow and ballistic movements for surveying the visual world. We have known since Hans Berger's work that, under these conditions, large-amplitude, rhythmic alpha waves appear above the visual (occipital) cortex. Eye closure and cessation of eye movements "release" rather than trigger the oscillation because there is not a single "cause" for the occurrence of the activity. The occipital alpha rhythm is regarded as the archetypal cerebral rhythm. Alpha oscillations are cortically widespread and regionally attenuated by a diverse range of specific and nonspecific stimuli and behaviors. The ongoing occipital alpha oscillation can be promptly and consistently blocked by various manipulations, such as eye opening, eye movement, visual imaginary, and even mental activity, such as arithmetic calculations. Although alpha activity is most prominent above the visual areas,[46] oscillations in the alpha frequency band can be recorded over a large part of the cortex, for example, over the frontal eye fields. These cortical areas are in charge of controlling eye movements. The relative independence of the occipital and frontal alpha oscillations is illustrated by their different frequencies: alpha waves are faster at occipital and slower at more anterior recording sites. The traditionally defined frequency range of the alpha band is from 8 to

44. Jouvet (1999, 2004) popularized the term "paradoxical sleep" referring to the fact that the electrographic patterns are quite similar to the waking brain yet arousing the subjects is more difficult than during slow-wave (non-REM) sleep. Grastyán and Karmos (1961) have independently discovered similar electrophysiological features, including hippocampal theta oscillations, in the cat, and attributed them to dreaming.

45. If the environment remains stable, the prediction is that sleep patterns and spike content of sleep-associated oscillations will remain similar. In support of this prediction, the firing rates of simultaneously recorded hippocampal neurons remained distinctly similar for at least 12 hours, during which time the rat experienced several wake/sleep cycles in its home environment (Hirase et al., 2001).

46. The most comprehensive source of human rhythms is the EEG atlas of Niedermeyer and Lopes da Silva (2005).

12 hertz. However, individual variations are quite large, and the mean frequency of alpha varies as a function of age, gender, and even intelligence. It is quite low in frequency in the infant human (< 7 hertz), reaches its maximum in young adulthood, and declines with age.

A rhythm that is similar to occipital alpha in frequency and, perhaps, in mechanisms can also be recorded above the sensory-motor cortical area. However, the conditions that give rise to this rhythm are quite different. It is indifferent to the presence or absence of visual input but requires immobility of skeletal muscles.[47] Conversely, it can be blocked by simply clenching the fist or by just moving a finger or a toe. Its waveform is also different, and its slightly spiky and arch-shaped morphology resembles a series of the Greek letter mu (μ), hence its most frequently used name: mu rhythm. The pattern has been "rediscovered" numerous times by various investigators, which explains the multitude of terms that refer to the same motor-relaxation–associated rhythm (*en arceau,* arcade, comb, wicket). The less poetic terms "Rolandic," "central," and "somatosensory" alpha refer to the dominant cortical location of these oscillations on the banks of the Rolandic fissure.[48] Importantly, even in the case of a very simple movement, such as moving a finger voluntarily, attenuation of the mu rhythm begins approximately 2 seconds prior to the actual movement, indicating time-intense computation of a voluntary act. Alpha oscillation has also been observed in the supplementary motor area of the cortex.[49] This rhythm is usually coherent with the Rolandic mu rhythm, and both oscillations are replaced by low-amplitude gamma-frequency oscillation upon finger or wrist movement. The intrinsic and independent nature of the alpha rhythm in the supplementary motor area was first demonstrated by the selective suppression of local alpha upon "planning" of movement by Gert Pfurtscheller and colleagues at the University of Graz in Austria. In the absence of overt movement but "planning" to move, alpha and mu rhythms could be topographically dissociated. Furthermore, high-spatial-resolution studies have demonstrated that mu synchrony can be selectively attenuated in a somatotopic manner. Isolated movement of the finger, thumb, foot, or tongue blocks the oscillation in the

47. Immobility can exert an effect on the activity of the somatosensory cortex in two different ways. When a skeletal muscle contracts, the state of the muscle is reported to the somatosensory pathways by the so-called muscle spindle receptors and stretch sensors in the tendons. A motor command, generated in the motor cortex, eventually contracts or relaxes the muscles, and these changes are registered by the somatosensory system. In a more direct way, motor neurons can affect neuronal activity in the somatosensory cortex even when the peripheral outputs and inputs are severed. These intracortical pathways are poorly understood, but since the works of von Holst and Mittelstaedt (1950) and Sperry (1950), it has been believed that this *reafferenz prinzip* or corollary discharge is critical for discriminating sensations due to our own movements from those that arise from the changing world around us.

48. The Rolandic fissure is the major sulcus that separates the frontal and parietal lobes. It separates the primary sensory and the primary motor gyri.

49. The supplementary motor area (Brodmann area 8) is the area anterior to the primary motor cortex that is important in temporal (sequence) organization and initiation of movements.

corresponding somatosensory area, whereas the surrounding areas can show increased power of mu oscillation.[50]

Using MEG, Riitta Hari and colleagues at the Helsinki University of Technology discovered yet another rhythm in the alpha band above the auditory (midtemporal) cortical region. They called it the "tau" rhythm, referring to its temporal cortical origin. The tau or third alpha rhythm is not affected by visual or somatosensory stimulation or by eye or hand movements but can be effectively blocked by acoustic stimulation.[51] Although the frequency and wave shape of the different alpha rhythms vary somewhat, their critical common denominator is that they emerge spontaneously in the specific sensory and motor areas of the cortex and first-order thalamic nuclei in the absence of relevant sensory inputs and motor outputs.[52] They can occur in isolation and be selectively attenuated by appropriate stimulation, indicating that cortical regions associated with different sensory modalities can sustain input-specific activity in relative isolation. In summary, alpha oscillation is a physiological reflection of the unperturbed state of first-order thalamic nuclei and their primary sensory and motor cortical partners. The isolated blockade of alpha activity in the areas involved in sensation and action convincingly illustrates the division of labor in the cerebral cortex. Collectively, these observations suggest that the first- and higher- order thalamocortical systems differ not only in terms of their anatomical connectivity between thalamic nuclei and cortical areas and their selective GABAergic control by the reticular nucleus and the zona incerta system but also in terms of their large-scale physiological behavior: the ability to generate alpha oscillations.[53]

Origin of Alpha Rhythms

In contrast to the well-studied and well-understood behavioral correlates of alpha oscillations, no firm explanation exists regarding their genesis. Two major classes

50. Pfurtscheller and Berghold (1989), Pfurtscheller (1992), Andrew and Pfurtscheller (1996), and Manganotti et al. (1998). These findings with scalp recordings have been confirmed by subdural electrode grids in patients (Arroyo et al., 1993). However, Crone et al. (1998), also using subdural grid recordings, did not find spatial topography. In their study, movement resulted in widespread desynchronization, including the ipsilateral somatosensory cortex. Pfurtscheller et al. (2000) suggested that topographical selectivity is visible only in the upper band (10–12 per second) of the mu rhythm, whereas nonspecific, widespread attenuation is evoked by movement in the lower (8–10 per second) frequencies.

51. The findings of Lehtela et al. (1997) support the existence of a distinct, reactive auditory rhythm in the human temporal cortex. Monaural bursts of white noise selectively blocked oscillatory 6.5–9.5 hertz MEG activity, with sources in the superior temporal lobes.

52. Using independent component analysis, Makeig et al. (2002, 2004) differentiated between posterior and central alpha rhythms and left and right mu rhythms. Children show reduced anterior power of alpha and reduced coherence between anterior and posterior electrodes in comparison to the adults (Srinivasan, 1993).

53. There seems to be a reciprocal relationship between spindles and alpha oscillations. Alpha oscillations are confined mainly to the first-order thalamocortical systems, whereas spindles dominate

of hypotheses can be distinguished as attempts to explain their origin. "Pacemaker" models, favored mostly by neurophysiologists,[54] assume that alpha oscillations arise from the endogenous rhythmicity of cortical or thalamic neuronal populations, which entrain other thalamocortical partners. Models in the second class of hypotheses assume that such oscillations emerge from the synaptic coupling of distributed populations of neurons and that no single group is responsible for the rhythm. The oscillation emerges in the context of a limit cycle or deterministic chaos or is a consequence of linearly filtered noise by some time constants and nonlinear amplification property of the system. All these computational models have some experimental support, but in general, they are too vague to pinpoint specific mechanisms and apply to a large set of oscillations not only alpha.[55]

The occipital alpha rhythm is prominent in animals with saccadic eye movements, large visual cortex, and binocular frontal vision, but it is virtually absent in the rat—the most extensively studied laboratory animal—and other nocturnal species. This absence is perhaps the major reason why we know so little about the mechanism of its generation. Most of the early work in this field was done on anesthetized cats in Andersen's laboratory and in behaving dogs in Fernando Lopes da Silva's laboratory in the Institute of Medical Physics, Utrecht, the Netherlands. Simultaneous recording from thalamic lateral geniculate nucleus and occipital cortex showed highly coherent field and unit activity between the two structures, suggesting the involvement of thalamic mechanisms. Recent *in vitro* work on the ferret and cat thalamus further supports the critical role of the

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mainly the higher order systems. This physiological dichotomy may be related to the reciprocal fMRI signals in the parietal-prefrontal "attentional" system and sensorimotor cortical areas (Greicius et al., 2003; Fox et al., 2005).

54. The strict definition of pacemaker is that its clock function is entirely determined by internal mechanisms without any external feedback. However, it may rely on some external "activation" or energy, but such input should not directly contribute to the phasic output of the pacemaker. E.g., a battery for a watch or an ambient neurotransmitter(s) for neuronal groups is not considered feedback. Brain networks, however, are complex feedforward and feedback systems, and too often it is not easy to distinguish between the "energizer" and rhythmic feedback provider role of recurrent pathways.

55. Norbert Wiener (1961) speculated that the human alpha rhythm is a result of coupled nonlinear oscillators. Lopes da Silva et al. (1974, 1980, 1997) and Nuñez (1998, 2000) suggest that cortical networks act as a band-pass filter at alpha frequency driven by a temporal brown noise. The random walk feature of brown noise would be responsible for the aperiodic nature of alpha trains. These theories do not address the source of noise, however, even though noise is of the essence in these models. The general model of Kelso and Fuchs (1995) assumes that brain activity displays trajectories, characteristic of Shilnikov chaos. However, the high expectations generated by early reports of low-dimensional chaos in the brain (e.g., Babloyantz et al., 1985; Freeman, 1992; McKenna et al., 1994) have not been backed up by strong experimental support. Other experiments indicate that alpha rhythm is often indistinguishable from linearly filtered noise (Stam et al., 1999; Gebber et al., 1999). See also other models by Jirsa and Haken (1996), Robinson et al. (1998), Stam et al. (1999), and Liley et al. (2002), and for a recent review, see Nuñez (2000).

thalamus in occipital oscillations.[56] Alpha-like activity has been also observed in the sensorimotor cortex of the cat, in synchrony with neuronal discharges in the ventralis posterior thalamic nucleus. Although the different investigators refer to this rhythm as somatosensory rhythm or postreinforcement synchronization, the frequency, waveform characteristics, and immobility dependence of the oscillation indicate strong homology with the human mu rhythm.[57]

In contrast to vision, rodents have an elaborate somatosensory representation. The face whisker system has an orderly and large representation in both the thalamus and sensory cortex.[58] Therefore, on the basis of evolutionary continuity, one expects to see a rhythm analogous to the human mu rhythm in rats. And there is one. In fact, the best-organized oscillation in the neocortex of the rodent is a waking immobility-related rhythm of 6–10 per second, with its largest amplitude over the somatosensory cortex. Because of its particularly large amplitude, I called it the high-voltage spindle (HVS). Its spike-and-wave form shares more similarity with the human mu rhythm than with the more sinusoid occipital alpha. Like in the cat, episode duration can vary from seconds to tens of seconds during immobility, but the rhythm disappears promptly at the onset of spontaneous or evoked movement or by stimulation of the whiskers or other body parts. As is the case for all alpha rhythms in humans, HVS also disappears during sleep.

The long-term dynamics of HVS are quite complex, with trains of HVS recurring rhythmically at 10–30 seconds and 15–30 minutes. Studies on HVS revealed the elaborate and widespread mechanisms involved in the regulation of thalamocortical rhythms. Units in the reticular thalamus as well as in the somatosensory and motor thalamic nuclei are entrained to the spike component of HVS. Neurons in the neocortex, striatum, pallidum, cerebellum, locus ceruleus, and other brainstem nuclei may also be recruited intermittently. Unilateral damage to the reticular nucleus can completely abolish the rhythm in one hemisphere, leaving the

56. The classical monograph of Andersen and Andersson (1968) described mostly experiments done under anesthesia, and the mechanisms described therein may be more relevant to sleep spindles than to alpha oscillations. For experiments in dogs, see Lopes da Silva et al. (1974, 1977l 1978, 1980; Lopes da Silva and Storm van Leeuwen, 1978). Hughes et al. (2004) suggest that metabotropic mGluR1a receptor activation of thalamocortical neurons and their gap junction coupling are parts of the alpha-promoting mechanisms. Work from McCormick's laboratory has been mostly dedicated to sleep spindles, but they may also be relevant to occipital alpha oscillations (McCormick and Bal, 1997).

57. Tadeusz Marczynski also found a reliable positive correlation between the magnitude of "postreinforcement synchronization" (i.e., mu rhythm) and the number of training sessions required for learning to press a lever for milk reward (Rick and Marczynski, 1976). He also showed that light or eye closure is not required for the occurrence of the rhythm. The alpha enhancement discovered by Marczynski is evident in many recent reports (e.g., Fries et al., 2001b). For a review of mu rhythm in the cat, see Rougeul-Buser and Buser (1997).

58. One of the most beautiful anatomical demonstrations of topographic representation in the cortex is the "barrel" organization in rodents (Woolsey and Van der Loos, 1970). Each barrel in the primary somatosensory cortex and barreloid in the ventral posteromedial thalamus corresponds to an identified whisker on the face, much like the orderly representation of fingers and other body parts. For a review, see Miller et al. (1991), Kossut (1992), Swadlow (2002), and Petersen (2003).

expression of HVS in the other hemisphere intact.[59] Nevertheless, the reticular nucleus cannot be regarded as a true pacemaker because its activity profoundly depends on the excitatory inputs from thalamocortical and corticothalamic neurons.

The currents associated with HVS in the neocortex are quite complex, of which only a very small portion reflects the synaptic activity of thalamocortical neurons. Instead, the thalamic inputs are strongly amplified, and the current distribution reflects mostly the activity of intracortical neuronal activity. In the simplest interpretation, it appears that the thalamus supplies the rhythm whereas the currents arise mainly as a result of intracortically organized patterned interactions among the various layers. Because the intracortical activity patterns are not strictly coordinated in time and because both first-order and higher order thalamic nuclei are involved, the various combinations of the multiple field dipoles give rise to a substantial wave shape variability of HVS (figure 7.6). So what appears as a relatively uniform mean field on the brain surface is actually a combination of numerous subpatterns that can be appreciated and analyzed only by simultaneously monitoring of all cortical layers.

The strong intracortical activation, associated with HVS, gives rise to a supersynchronous rhythmic discharge of neurons in multiple cortical layers and a short-lived ultrafast rhythm (300–600 per second).[60] Assuming that similar mechanisms are at work for the occipital alpha and auditory cortical tau oscillations, we can conclude that these rhythms arise as a result of a complex interaction between the GABAergic thalamic neurons and thalamocortical neurons combined with neocortical amplification of the thalamic signals. All these steps are necessary parts of the oscillatory machinery. Given the dominance of alpha-type oscillations in the circuits involving the first-order thalamic nuclei, we can conclude that the extent of alpha oscillations is an indication of the cortical disengagement from inputs of the body and the environment.

Disconnection from some aspects of the environment is by no means an indication of decreased brain performance. We also have to emphasize that alpha oscillations are not sleep patterns. The alpha peak in the human scalp EEG power spectrum is prominent under virtually all waking conditions, not only when eyes are closed and muscles are relaxed, although these conditions robustly increase the power in the alpha band. The "idling" hypothesis of alpha oscillations explains the waking alpha peak in the EEG by assuming that not all sensory areas are active all the time. Eyes or skeletal muscles are not moving constantly, and alpha may build up in some intervening periods. When cortical columns are involved in processing

59. Semba and Komisaruk (1980) were the first to use the term "mu" in the rat. For reviews, see Buzsáki et al. (1990). For sensory perturbation of HVS, see Wiest and Nicolelis (2003). These authors also emphasize the similarity between HVS and mu rhythm in humans. Buzsáki et al. (1991), Nicolelis et al. (1995), Kandel and Buzsáki (1993), and Berke et al. (2004) illustrate phase-locked unit activity in numerous brain structures.

60. Ultrahigh-frequency ripples (300–600 hertz) are present during both HVS and sleep spindles (Kandel and Buzsáki, 1997) as well as epileptic discharges (Grenier et al., 2001). Ripples in the somatosensory cortex can also be evoked by somatosensory stimulation in both rats (Jones and Barth, 1999) and humans (Curio et al., 1994).

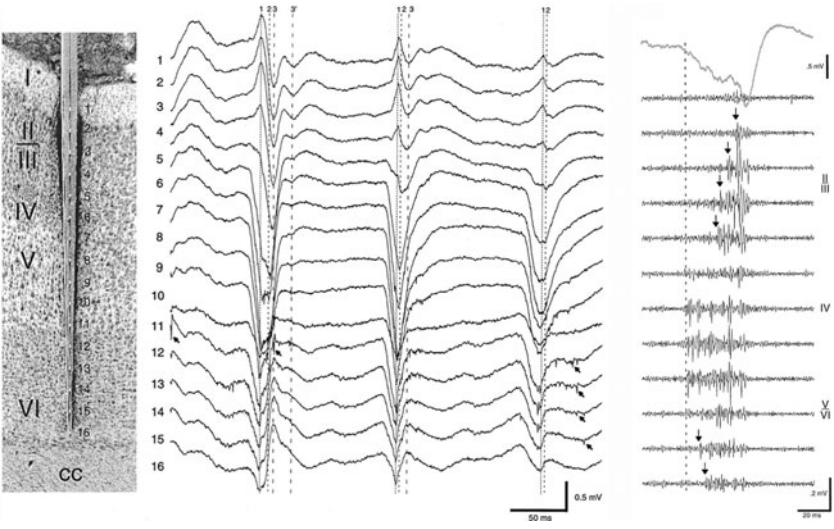

Figure 7.6. Somatosensory "alpha" (mu rhythm) oscillations in the rat consist of multiple time-shifted dipoles. Left: Location of the silicon probe and the recording sites in relation to the different cortical layers. Middle: Three cycles of an HVS episode. Vertical lines indicate the presence of at least three putative dipoles contributing to the fast component of the oscillation with different depths of phase reversal. Dipole 3 was occasionally observed as a separate event (3′). Right: Vertical spread of multiple unit from layer 5 to superficial and deep layers during the fast component of dipole 3. Most cortical oscillators consist of multiple, time-shifted dipoles, as illustrated here. Because of its high amplitude and waking-immobility correlate, the rhythm shown in the figure is called high-voltage spindle (HVS) to distinguish it from sleep spindles. However, both depend on the integrity of the reticular nucleus of the thalamus, and both consist of multiple dipoles (Steriade and Deschênes, 1984; Buzsáki et al., 1988). Reprinted, with permission, from Kandel and Buzsáki (1997).

inputs from the legs, other columns can stay disengaged and produce alpha oscillations. This "off-duty" hypothesis, therefore, suggests a very strict temporal relationship between sensory processing, motor activity, and the suppression of alpha waves. However, it cannot explain why, in various cognitive tasks, alpha power increases with task difficulty (see Cycle 12). An alternative hypothesis is that self-organized alpha oscillations are a reflection of internal, mental operations. Cycle 8 provides ample examples of such internal processes.

In summary, sleep- and rest-associated oscillations are the best examples of self-organized operations in the brain. The trajectory of state changes in neuronal space is predictable from the history of previous sleep states, indicating the deterministic dynamics of sleep. Nevertheless, very little is known about the mechanisms that force the brain to change and stabilize its trajectory of activity and even fewer experimental data are available about the neuronal content of these state changes. It is expected that the initial conditions (i.e., waking experience superimposed on the past history of brain circuits) can affect both the state variables that

govern the evolution of sleep stages and the ensemble spike patterns that underlie these states. What is the empirical evidence for such conjecture? Read on.

Briefly . . .

The thalamus is a hub for the neocortex that provides functional shortcuts between the vast areas of the cerebral hemispheres and reduces the synaptic path lengths between the various cortical areas. Both the excitatory thalamocortical and the inhibitory neurons of the reticular nucleus are endowed with various intrinsic conductances, which promote oscillations at various temporal and spatial scales. First-order and higher order nuclei of the thalamus have reciprocal relationships with sensory and associational cortices, respectively. Such a dichotomy of thalamic organization is also reflected in the differential inhibitory control of higher order nuclei by a large set of extrathalamic structures.

In the absence of environmental inputs, the brain gives rise to self-organized activity that follows a complex trajectory in time and neuronal space during sleep. The extent of thalamic and neocortical involvement varies in the different oscillations of sleep. The isolated neocortex or small pieces of the neocortex alone can sustain self-organized patterns. Neurons in local or global regions of the cerebral cortex rapidly swing between excitable and less excitable (up and down) states. In the intact brain, properly timed exogenous influences (e.g., external sensory or body-movement–associated signals during sleep) can trigger upswing changes, provided that the cortical network has already spent a sufficient amount of time in the down state. The persistent activity in the up state is due to a balanced recurrent excitation and inhibition. The network-generated buildup of intracellular Ca^{2+} and Na^{+} activates a K^{+} current, which together with increasing efficacy of inhibition terminates recurrent activity and brings the network back to silence.

The average length of the down state increases as sleep deepens. The down states are reflected as positive waves in deep layers and negative deflections in scalp and superficial cortical layer recordings. These silent epochs are the delta waves of slow-wave sleep. The silent periods are associated with increased K^{+} conductance that can be blocked by various subcortical neurotransmitters. The neuronal synchrony, associated with the down-up depolarization shift, is reflected in the field and scalp recordings as a K-complex. Parallel with the increasing probability of cortical up-down state shifts, the membrane potential of thalamocortical neurons progressively polarizes. Due to specialized voltage-gated channels in thalamocortical and reticular neurons (I_T, I_h, and I_{CAN}), the up state shift can either trigger sleep spindles or induce dominant delta activity.

The strong cholinergic activity during REM sleep and in the waking brain is mainly responsible for the lack of down states in cortical neurons. The most prominent oscillation of the waking brain is the family of alpha rhythms that occur selectively in every sensory and motor thalamocortical system in the absence of sensory inputs. Nevertheless, alpha oscillations are not simply a result of sensory disengagement but may reflect internal mental processing.

Cycle 8

Perturbation of the Default Patterns by Experience

> With regard to sleep and waking, we must consider what they are: whether they are peculiar to soul or to body, or common to both; and if common, to what part of soul or body they appertain.
>
> —Aristotle, *On the Soul*

Aristotle could not care less about the brain.[1] Nevertheless, even if we substitute or equate the soul with brain mechanisms, the question is as puzzling today as it has been for the past 2,400 years: do our daytime experiences determine the exact trajectory of sleep the following night, or does the self-organized process of sleep determine how the waking brain reacts to environmental perturbations? It was conjectured more than a century ago that learned material remains in a fragile state after the experience but strengthens over time, and sleep is suspected to be responsible for the consolidation process.[2] Ever since the discovery of REM sleep in 1953 and its association with its subjective content, dreaming, this peculiar stage of the sleep cycle has been believed to be responsible for the consolidation effect. Because dreams have been thought to incorporate events of daily life since

1. See Cycle 1 for the discussion of Aristotle's view on the heart and brain.

2. Memory, in its widest definition, is neuronal representation of past experiences that persists over time. Consolidation of memory is a hypothetical construct referring to the progressive stabilization of the memory trace in long-term storage. A metaphor often used to illustrate this concept is the development of a photograph. Taking a picture corresponds to the encoding process, and the chemical development of the image is consolidation. The memory trace may be rekindled by rehearsal, recall, associations, or dreaming (Squire, 1992; Squire and Zola, 1998; McGaugh, 2000; Nader et al., 2000; Sara, 2000; Dudai and Eisenberg, 2004) and strengthened repeatedly. In general, actualization of the same coherent spatiotemporal pattern of neuronal activity or recreation of a neural attractor responsible for the specific assembly patterns provides the necessary conditions for the plastic changes required for

ancient times, it was logical to assume that rehearsal of learned information in dreams could make repeated use of the brain hardware during REM sleep.[3]

Although initially large numbers of experiments, primarily involving a "selective" REM sleep deprivation design, seemed to support the critical role of REM in memory consolidation, the technical and theoretical problems with those experiments have begun to surface in the past two decades. First, the forebrain patterns of activity of REM sleep are quite similar to those of the waking brain.[4] So one wonders what special processes are at work in REM that cannot happen in the waking brain. Second, by physical means it is impossible to selectively deprive the brain of REM sleep without affecting the whole sleep process because sleep is a dynamic process. The techniques used to deprive the brain of REM sleep are quite stressful, and therefore, stress could be the explanation for the performance deficit after perturbed sleep.[5] Third, a large body of clinical literature shows that millions of patients on antidepressants that decrease, and in some cases eliminate, REM stage do not complain of striking memory problems.[6] Finally, there is a theoretical problem: where does the memory trace reside between waking experience and the emergence of REM sleep?[7] The experiments discussed in this Cycle

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the stabilization or reparation of the trace. Retrieval of memory traces not only can strengthen them but also can make them vulnerable each time they are recalled. The fragile nature of the trace and its modifiability by the multiple stabilization processes are the fundamental neurophysiological reasons for our "untrustworthy" memories (Loftus, 1997). For a very readable history of twentieth-century memory research, see Milner et al. (1998).

3. The impact of Freud's *The Interpretation of Dreams* (1900) is hard to dismiss even today. Aserinsky (1996) and Gottesman (2001) are perhaps the best descriptions of the discovery and history of REM sleep. For recent physiological works in favor of REM sleep's role in memory consolidation, consult Winson (1990, 1993), Pavlides and Winson (1989), Karni et al. (1994), Smith (1995), and Louie and Wilson (2001).

4. There are, of course, differences between REM and the waking brain. E.g., several subcortical neuromodulators (serotonin, norepinephrine, histamine, hypocretin) reach their highest and lowest levels of release during waking and REM, respectively. However, these and other known differences do not explain why REM would be special for memory consolidation (Macquet and Franck 1996).

5. REM sleep deprivation by physical means refers to waking the subject every time some REM sleep is detected. In small animals, the "inverted flower plot" method is used most frequently: a small platform is placed in a water tank, and every time the animal loses its muscle tone at the onset of REM, it falls into water. Obviously, after waking, the subject does not immediately return to the same stage of non-REM; thus, the procedure is not selective.

6. It has been also conjectured that sleep, and particularly REM sleep, serves to stimulate those synapses that were not sufficiently used during wakefulness to maintain their synaptic connections (Fowler et al., 1973; Krueger et al., 1995; Kavanau, 1997). Accordingly, neurons in REM sleep may discharge randomly and erase synaptic modifications brought about by the waking brain (Crick and Mitchison, 1983). For a criticism of REM sleep as a sole mechanism of memory consolidation, see Buzsáki (1998), Vertes and Eastman (2000), and Siegel (2001).

7. I suggested that "idling" patterns and non-REM sleep that are contiguous with waking experience are essential for memory consolidation, rather than REM sleep (see Cycle 12), on the basis of the electrophysiological similarities of assembly patterns between non-REM sleep in the hippocampus and the requirements of synaptic plasticity (Buzsáki, 1989). Numerous studies support this two-stage scenario (Wilson and McNaughton, 1994; Stickgold et al., 2001; Destexhe and Sejnowski, 2001; Hobson and Pace-Schott 2002; Steriade and Timofeev, 2003; Born and Wagner, 2004; Ribeiro et al., 2004). However, see criticism by Vertes and Eastman (2000), Siegel (2001, 2005) and Tononi and Cirelli (2006).

aim to illustrate that the deterministic patterns of sleep and rest can be perturbed by waking experience. After each day's experience, however, the brain falls back to the default pattern to rerun and intertwine the immediate and past experiences of the brain's owner.

Behavioral Effects of the Self-Organized Oscillations of Rest and Sleep

We spend one-third of our life in sleep, a major part of which is non-REM sleep. There must be a good reason why complex brains have developed an elaborate choreography of periodically recurring sleep stages. Indirectly, the importance of sleep is illustrated by the fact that the metabolic cost of maintaining brain activity is only slightly reduced during sleep, and in many, nonsensory, parts of the brain, the energy cost rivals with that of the waking brain.[8] Even in hibernating animals, brain metabolism remains relatively high.

Sleep is characterized by strong synchrony of neuronal activity, brought about by the prominent oscillations of the various stages of the sleep cycle. Unfortunately, very few empirical findings are available on the neuronal content of sleep oscillations. Extrapolating from experiments on the hippocampus (Cycle 12), let us assume that the neuronal content of thalamocortical oscillations of rest and sleep is influenced by waking experience.[9] If so, the repeated activation of the same neurons and synapses after the initial experience could be useful because the molecular processes, underlying strengthening and weakening of synaptic connections between neurons, are quite protracted in time.[10] Sleep could hold the information for the time required for the slow molecular mechanisms by replaying chunks or fragments of the information learned in the waking state.

However, even if convincing evidence is provided by future studies regarding the similarity of neuronal ensembles in the waking and sleeping neocortex, these observations alone cannot be considered as compelling evidence for the essential role of sleep oscillations. Nevertheless, physics and computational modeling might provide some clues why brain rhythms can be useful in this hypothetical mechanism. Harmonic oscillators are excellent storage devices because the long-

8. Synaptic modification during sleep cannot be the whole story, though, since it does not explain the serious consequences of sleep deprivation. According to recent views, sleep corrects hypothetical metabolic deficits that build up during waking (Borbely, 1998; Borbely and Tobler, 1989; Greene and Siegel, 2004). Vertes (2004) suggests that the role of REM sleep is to provide periodic stimulation to the brain and promote recovery from sleep. If this were they case, then patients on antidepressants and reduced REM sleep (Vertes and Eastman, 2000) would have problems waking up, which is not the case. For metabolic changes of brain areas during sleep, see Macquet and Franck (1996) and Hofle et al. (1997).

9. For the consolidation hypothesis of memory trace in the thalamocortical system during sleep, see Steriade and Timofeev (2003) and Destexhe and Sejnowski (2001).

10. For a concise summary of the multitude of molecular biological changes associated with synaptic plasticity, see Kandel and Squire (2000) and Bliss and Collingridge (1993).

term behavior of the oscillator can be reliably predicted/recalled by short-term observations. Let me draw support for this argument from the simplest case, a network of randomly connected neurons in which oscillations can be turned on and off. Once the oscillation is turned on, participation of neurons and their sequence of activity depend only on the connectivity and the starting conditions. In a noise-free system, the sequences of neuronal activity will repeat reliably and infinitely. Remember those annoying repetitions in your old gramophone record when the needle kept slipping back to an outer groove? Unless the oscillation is perturbed (the needle is moved manually into another groove), the pattern in an oscillating network repeats itself infinitely. This is an important observation because it implies that the initial conditions can be reliably recreated from the repeating sequences of spike patterns even in the presence of occasional synaptic transmission failures. Restarting the population activity with the same initial condition thus leads to the very same sequence of spike patterns. A pertinent example is petit mal epilepsy, characterized by a regular 3-hertz spike and wave discharge in the thalamocortical system, followed by an immediate recovery of neuronal activity. A sentence interrupted by the onset of the spike and wave pattern that may last for seconds or even long minutes, is often continued at the offset of the seizure (Herbert Jasper, personal communication). The possible explanation for this puzzling phenomenon is that the initiating condition that gives rise to the rhythm is "frozen" into the deterministic oscillation which can be regained at the offset.

The situation becomes a bit more complex if the ongoing oscillator is perturbed transiently. Now, the new sequence will reflect the combination of the initial conditions and the perturbation (see extended discussion in Cycle 12).[11] With some leap of faith, we can speculate that daily experiences that perturb the internal dynamics of the brain leave their marks. When the brain is left unperturbed during sleep, the modifications in synaptic connections and channel distributions, brought about by our daily waking routines, are "frozen" into the self-organized oscillations of the various sleep stages. This is possible because sleep is a deterministic process. Because various oscillatory patterns evolve through the various stages of sleep, the dynamics of the neuronal replay are expected to vary over time as well. To date, very little is known about the hypothetical scenario of experience-induced neuronal patterns during sleep in the thalamocortical system.

The lack of hard physiological evidence for the experience-related content of sleep did not prevent curious psychologists to test the real-life implications of the two-stage model of memory consolidation. To date, Jan Born at the University of Lübeck in Germany has provided the most compelling support for the critical role of non-REM sleep in memory formation.[12] Using both visual texture discrimination

11. Gerstner and Kistner (2002) provide numerous inspirations for future research on this topic. Their simulations show how the initiating conditions can be recovered after many oscillatory cycles.

12. It is important to emphasize that "memory" is not a unitary term and has several forms that depend on different brain mechanisms. Declarative memories include events of one's past (episodic memory) and general (semantic) knowledge that can be "consciously" retrieved and declared. Declarative memories are believed to depend on the hippocampal-entorhinal system. Other forms of memories

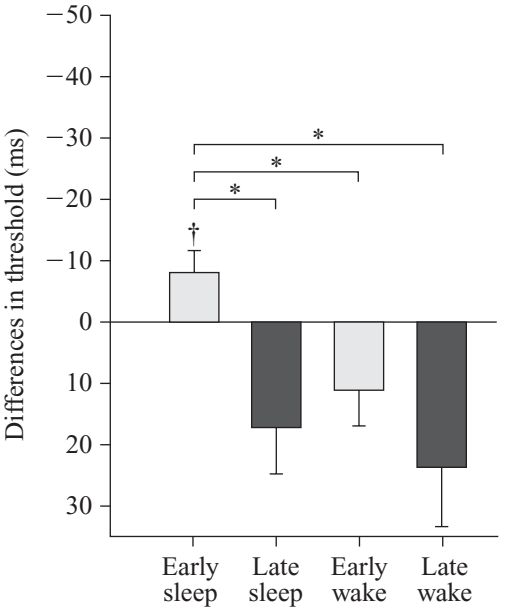

Figure 8.1. Slow-wave sleep facilitates memory. Subjects either slept for 3 hours during the retention interval of a visual discrimination task or were kept awake throughout the time interval. Only early-night sleep rich in slow-wave sleep improved performance. Asterisks indicate significant group differences. Dagger, significant improvement relative to chance performance. Reprinted, with permission, from Gais et al. (2000).

task and paired word association task (e.g., bone/dog) in different experiments, his team found substantial improvement in performance after sleep. Importantly, they showed that improvement was due primarily to the first 4 hours of night sleep, rich in stage 3 and 4 events, and much less on late-night sleep, dominated by superficial stages and REM (figure 8.1). Similarly, Robert Stickgold and colleagues at Harvard Medical School found that the magnitude of memory enhancement after sleep was positively correlated with the amount of early-night slow-wave sleep, although it as also correlated with late-night REM sleep. Moreover, behavioral performance also increased after a daytime nap, which is dominated by slow-wave sleep.[13]

Perhaps the most spectacular result in this area of research is the demonstration of sleep facilitation of creative insight. Did you ever wake up with the right answer to a problem that you could not solve the night before? To bring this folk

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depend on other systems, e.g., the cerebellum, striatum, or amygdala, and cannot be retrieved "consciously" and include procedural skills and habits (e.g., how to ride a bicycle or to pronounce words) and emotions (Tulving, 1972, 2002; Squire, 1992; LeDoux, 1996; Eichenbaum, 2002).

13. Gais et al. (2000), Gais and Born (2004), Stickgold et al. (2001), and Mednick et al. (2002). For a review of imaging studies on sleep and memory, see Maquet (2001).

psychology belief into the lab, Born's team asked their subjects to generate number sequences that included a hidden rule—the second sequence was identical to the last in the series. Uncovering the hidden rule was possible only after several trials. The subjects were given only two trials before going to bed, not knowing about the hidden rule. A night's sleep triggered insight of the rule the following morning in most subjects, whereas the same amount of time spent in waking during the day had little effect. These experiments provided the first controlled laboratory experiments for the widely known anecdotes of several famous scientists, writers, and musicians that sleep catalyzes the creative process.[14] The potential physiological basis of such associations are discussed in Cycle 12.

Perturbation of Self-Organized Patterns by Waking Experience

While the experiments discussed above show that a learned skill or performance of some memorized material improves after sleep, one might argue that it is simply the passage of time that causes the improvement. Although no such increase is present after the same number of daytime hours, one may conjecture that the expected time-related improvement is canceled by the interfering effects of subsequent waking activity. To make the case for sleep stronger, one should demonstrate some specific changes in sleep itself. We all know from experience that traumatic daily events noticeably affect our sleep. But do "regular," nontraumatic events also leave their trace on the macroscopic appearance of the sleep cycle? At least a handful of experiments suggest that this is indeed the case.

In an attempt to selectively stimulate a specific brain region, Alex Borbely and colleagues at the University of Zurich exposed the dominant hand to a prolonged vibration stimulus before sleep onset. After stimulation of the hand, the EEG power in the contralateral hemisphere showed a significant increase in the lower frequency band (between 1 and 10 hertz). As expected, the largest increase was observed at electrode sites overlying the sensory-motor cortex. An analogous result was obtained in the rat where unilateral whisker stimulation in the waking state induced an interhemispheric shift of low frequency EEG power in non-REM sleep toward the contralateral cortex (figure 8.2). A similar rationale was used in a subsequent experiment by Giulio Tononi and his team at the University of Wisconsin–Madison (figure 8.3). They asked their subjects to reach for visual targets from a central starting point using a handheld cursor connected to a computer. However, a trick was involved. An opaque shield prevented the subjects from monitoring their hand and arm movements. Unbeknown to the subject, the cursor position was rotated anticlockwise relative to the hand position by a fixed angle

14. Wagner et al. (2004). See Prelude, footnote 2 in Prelude, for Otto Loewi's dream about the vagus experiments; Strathern (2000) for Dmitri Mendeleev's insight into the periodic system; and Maquet and Ruby (2004) for sleep-induced insights reported by other famous people.

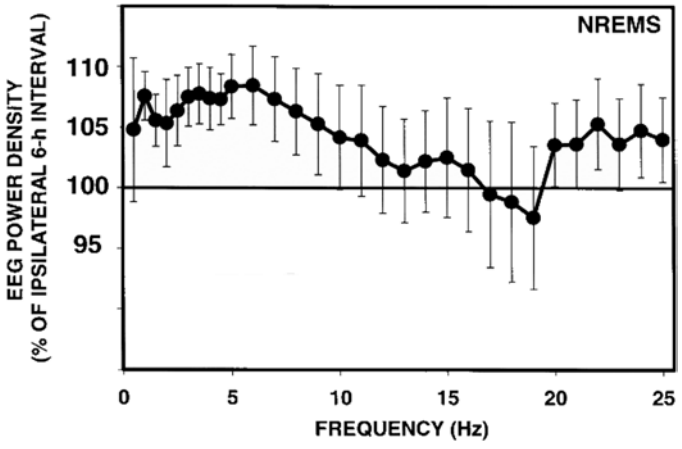

Figure 8.2. Waking experience modifies subsequent neocortical activity during subsequent sleep. Whiskers of rats were trimmed on one side of the face 6 hours prior to testing sleep patterns. EEG power density in slow-wave sleep increased in the hemisphere contralateral to intact whiskers relative to the power of the ipsilateral (control) hemisphere. NREMS, non-REM sleep. Reprinted, with permission, from Vyazovskiy et al. (2000).

while the subject executed the reaching task. Thus, this task was more than just repeating a well-trained movement. It required a complex eye–hand movement adaptation, which has been shown earlier to activate the contralateral parietal cortex. Immediately after the learning experience, scalp EEG was recorded by a 256-channel high-resolution system. This technical wizardry was critical because, as it turned out, the behaviorally induced changes occurred in a small cortical area. During the first cycle of sleep, the preceding practice induced a significant increase in the EEG power in a circumscribed part of the contralateral parietal cortex, leaving the remaining regions of the brain unaffected by the experience. Importantly, the investigators also showed that the local increase of low-frequency power correlated with the magnitude of sleep-enhanced performance in different subjects.[15]

Although these experiments indicate selective changes of EEG in spatially localized brain regions, they do not specifically address the involvement of particular rhythms. In other experiments, a selective increase of the number and power of sleep spindles was reported following spatial learning or intensive verbal learning. Moreover, the spindle density in stage 2 of sleep positively correlated with learning efficacy. In a related series of experiments, no task was given to the subjects, but differential distribution of sleep spindle density above the frontal cortical region across subjects was related to their intelligence quotient (IQ). A possible interpretation of the positive correlation between these measures is that the life-long experience that led to higher IQ was reflected by the higher prevalence of specific sleep oscillations. The reduced

15. Kattler et al. (1994), Vyazovskiy et al. (2000), and Huber et al. (2004).

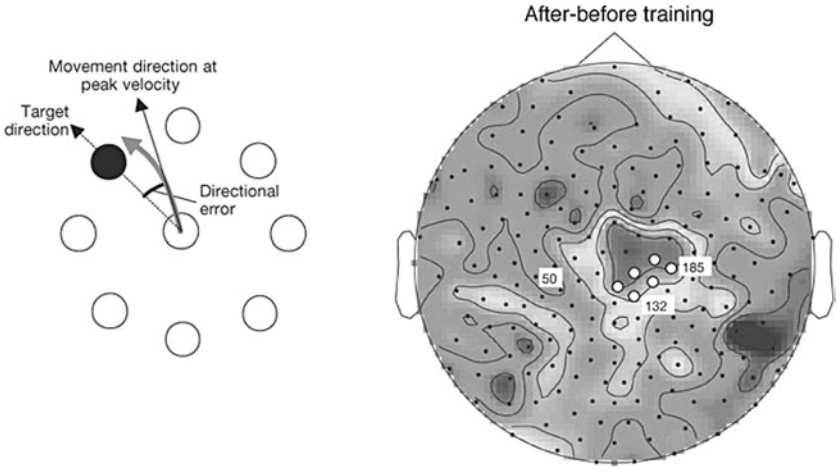

Figure 8.3. Learning produces specific and localized effects on sleep. Volunteers learned to reach for visual targets using a handheld cursor while unconsciously adapting to systematic rotations imposed on the perceived cursor trajectory before going to sleep (left). In a control session, subjects performed the same task without any imposed rotation. Right: Topographic distribution of the percentage change in delta power during non-REM sleep between the training and the control condition. White dots indicate the cluster of six electrodes over the right parietal areas showing significant increase of power. Modified, with permission, from Huber et al. (2004).

number of sleep spindles in demented patients adds further support for the possible functional link between self-organized oscillations and waking brain performance.[16]

Specific behavioral manipulations can produce selective changes in particular brain areas. Raising kittens and mice for 3–4 months in complete darkness seriously affects not only their visual abilities but also their sleep oscillations. Although the total time spent in sleep did not differ between dark-reared and control animals in these experiments, there was a selective decrease in delta power in the dark-reared group. Importantly, the reduction in delta power was confined largely to the visual cortical areas, and no such change was observed above the somatosensory cortex, pointing to the selective effect of visual experience on delta oscillation in the relevant cortical area. Interestingly, the effects were reversible because delta power returned to control levels 2 months after exposing the dark-reared animals to normal light. A more direct link between cortical plasticity and sleep has been provided by Michael Stryker at the University of California–San

16. Meyer-Koll et al. (1999), Gais et al. (2002), Mölle et al. (2002), Clemens et al. (2005), and Bodizs et al. (2005). Physiological changes during sleep in dementia and other diseases may, of course, be also explained by a common "third-party" mechanism that is independently responsible for both the disease and altered sleep patterns. Nevertheless, the correlations are indicative of possible links between sleep patterns and cognitive performance (Shinomiya et al., 1999).

Francisco. In normal cats, the amount of inputs from both eyes to the visual cortex is roughly equal. Closing one eye during early development dramatically shifts the balance of ocular dominance so that input from the covered eye is much less effective in driving visual cortical neurons than from the control eye. The effect is so robust that the shift in ocular dominance can be reliably demonstrated after only a few hours of eye closure. Stryker and colleagues closed one eye in 1-month-old kittens and let some of them actively explore in the light for 6 hours. A subgroup of kittens was examined for ocular dominance right after the experience. The kittens in the critical experimental group were allowed to sleep in the darkness for an additional 6 hours. Two more groups were involved to control for darkness and extended waking for 12 hours. The enhancement of plasticity, as measured by the magnitude of ocular dominance, was twice as large in the sleep group and in the 12-hour light-exposed group, compared to the control kittens with only 6 hours of monocular experience, even when followed by an additional 6 hours waking activity in the dark. In other words, the ocular asymmetry effect continued to grow during sleep to the same extent as prolonged light and pattern exposure. Importantly for our discussion, the magnitude of ocular dominance shift robustly correlated with the amount of non-REM sleep but not with REM episodes.[17]

Together, these experiments in laboratory animals and human subjects indicate that sleep and its rhythms provide a clear, regional indicator of sensory experience. These long-lasting changes may be brought about by reorganization of synaptic connections and strengths and/or by alterations of intrinsic conductances in neurons. Support for such structural changes of connectivity is also provided by MRI experiments. In the cerebral cortex of volunteers engaged in regular juggling exercises daily for 3 months, a significant enlargement of sensory-motor areas was observed, presumably due to more axonal connections. These findings therefore support to idea that waking experience not only affects the macroscopic aspects of sleep but also brings about structural changes.[18] If short-term experience has a measurable effect on sleep patterns and oscillations, long-term practice is expected to exert an even larger impact.

Long-Term Training of Brain Rhythms

Meditation-Induced Alpha Activity

Meditation is a widely practiced behavioral technique of tuning into your "inner self" but still remaining aware of the surroundings. The methods of meditation

17. Frank et al. (2001).

18. Draganski et al. (2004). These findings suggest the possibility that new axon collaterals are formed also in the adult. Imaging of white matter in professional piano players, however, indicates that practice in childhood is most critical for the establishment of intermediate- and long-range connections (Bengtsson et al., 2005). This may also apply to other long-range connections supporting high-level abilities.

depend on the philosophies they serve. With some simplification, Yoga emphasizes the "real" or superior reality within and devalues external reality, consistent with the beliefs of Yogic philosophy, in which the world around us is held to be a mere illusion, or Maya, in Sanskrit. Yoga meditation is typically practiced with the eyes closed so that the mind can fully concentrate on inner events. The ultimate goal of Yogic absorption into inner experience is to ignore stimuli from the world of the senses. In contrast, Zen philosophy does not deny the reality of the external world and seeks to build a harmony between the inner and outer worlds. Zen is practiced with the eyes half open, focused softly on some blurred object. It takes several years or decades to advance mind states from the beginner's mind, through *kensho,* culminating in *satori.* Brains of yogis and Zen practitioners, therefore, provide unexploited opportunities to examine the effects of long-term behavioral training on brain rhythms. Unfortunately, it is difficult to obtain consent of highly trained contemplative yogis and students of Zen to participate in laboratory experiments. Not surprisingly, quantitative studies are rare. Nevertheless, the available evidence is telling. When absorbed in the Samadhi of Yoga meditation, when the self-versus-environment distinction disappears, external stimulation is largely ineffective in blocking alpha oscillations, whereas continued blocking without habituation is observed in Zen meditators. Both types of practice increase both the power and the spatial extent of alpha oscillations, and the magnitude of changes correlates with the extent of training. Beginners show increases of alpha power activity over the occipital area, whereas in intermediate meditators the extent of oscillating cortical area is increased and the frequency of alpha oscillations is decreased. After decades of training, large-amplitude theta-frequency rhythm may dominate over a large extent of the scalp.[19] Yoga and Zen training, therefore, reflects a competition between internal forces of synchrony and external perturbation (figure 8.4).

Enhancement of Alpha Power by Sensory Feedback

Is spiritual experience a critical ingredient of the altered brain dynamics? Conversely, is alteration of oscillatory dynamics associated with behavioral performance? Believers of the "alpha movement" believe so. The reasoning is this: when our brains are dominated by alpha oscillations, we feel a sense of calm; therefore, increasing alpha activity will calm our agitated brain. The repeatedly observed correlation between various laboratory measures of spontaneous alpha oscillations and cognitive and memory performance[20] is a further rationale

19. For brain activity during Yoga meditation, see Wenger and Bagchi (1961), Anand et al. (1961), or Shapiro (1980); in Zen, see Kasamatsu and Hirai (1966), Kugler (1982), or Murata et al. (2004). The first time I saw a presentation on the scalp EEG of yogis at the World Congress of EEG in Amsterdam in 1977, I thought the recordings were from patients with generalized spike-and-wave epilepsy because of the large-amplitude, generalized pattern in some yogis. A recent study (Lutz et al., 2004) emphasizes the enhanced gamma power during meditation, perhaps reflecting the increased neuronal computation associated with the process of meditation.

20. Surwillo (1961) and Anokhin and Vogel (1996). For an informative review on the cognitive role and correlations of alpha oscillation, see Klimesch (1999).

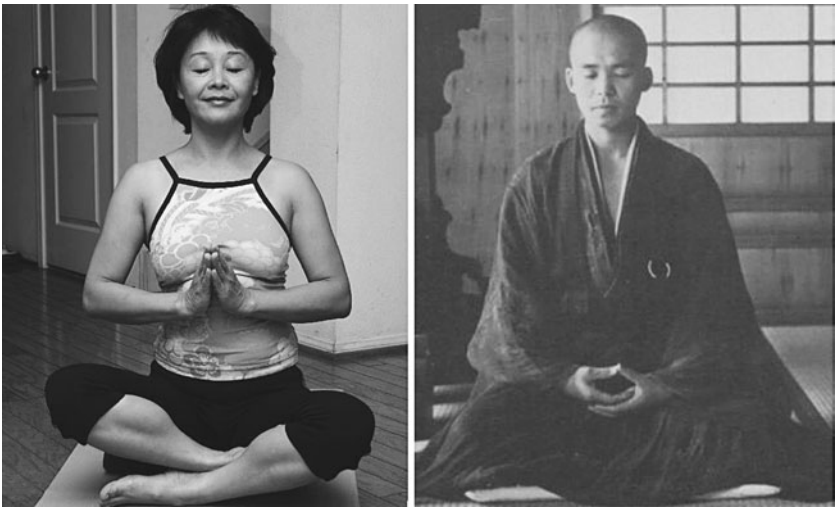

Figure 8.4. Extensive practice can change brain patterns. The goal of Yoga (left) and Zen (right) training is to fully engage the brain without sensory stimulation. Both training techniques reflect a competition between internal forces of oscillatory synchrony and external perturbation.

for changing spontaneous brain activity. The method suggested to achieve such goals is a hybrid of autogenic training and neurofeedback. The detected EEG patterns from the scalp are transformed into audio tones so that the subjects can recognize and monitor the occurrence of alpha waves online after minimum training. Alternatively, alpha power can be integrated over several minutes by an appropriate computer algorithm and fed back to the trainee. After several days of practice, practitioners can more readily drive their brains toward the alpha state. Yet another way of increasing occipital alpha oscillation is by entraining the waves by low-frequency light flashes. Entrainment works as long as the frequency of the second or third harmonic of the flashes does not deviate by more than 1–2 hertz from the "free-running" (i.e., spontaneous) alpha rhythm.[21] After about a week's training, significant increases of alpha power are observed even at more frontal sites, whose activity was not used for training. Occasionally, slowing of alpha frequency is also reported. Whereas it takes several years

21. See, e.g., Hardt and Kamiya (1978), Chernigovskii et al. (1982), and Moore (2000). Enhancement of alpha power to the stimuli is an illustration of network resonance at work. Resonance of thalamocortical network has been known for many decades. Electrical stimulation of the thalamus or its inputs at about 10 hertz results in potentiation of the evoked responses, whose dynamics differ with the site of stimulation. Repetitive stimulation of intralaminar thalamic nuclei induces the "recruiting" response (Demsey and Morison, 1942; Morison and Demsey, 1942; Jasper and Drooglever-Fortuyn, 1947; Clare and Bishop, 1956; Ralston and Ajmone-Marsan, 1956), whereas simulation of sensorymotor thalamic nuclei results in an "augmenting" response (Spencer and Brookhart, 1961; Morin and Steriade, 1981; Steriade, 2001b).

of Zen meditation to reach the stage of slowing the frequency of alpha and the spreading of alpha oscillations forward to more frontal areas, approximately the same results can be accomplished by a week's training with alpha feedback.[22]

Does an accelerated enhancement of alpha oscillations mean that there is a cheap way of getting relaxed and curing anxiety, for example? There is no simple answer. Unfortunately, most studies with both alpha training and meditation have been carried out on a small number of subjects, and placebo effects were seldom considered. More troublesome is the fact that the "alpha relaxation" training became commercialized before large-scale studies objectively examined its effects on brain and behavior. The commercialized alpha biofeedback therapy promised too much and delivered too little, and the alpha feedback "movement" went underground by the late 1970s. There is also a conceptual misunderstanding between the goals of relaxation therapy and mediation. Meditation is not about stress relief; it is an intense mental process with the goal of enhancing attention skills and visual imagination. Some yogis can to hold complex images in their minds for hours yet shift attention rapidly. A paradox is that enhanced alpha activity is taken as evidence for the brain's idling and relaxation in the brains of Westerners and a physiological correlate of enhanced "internal attention" in the brains of Buddhist monks. Obviously, this controversy is worth investigating. I attempt to address the relaxation versus attention correlation of alpha rhythm in Cycle 12.

Exploiting Brain Oscillations

Alpha or brain wave control has reemerged recently, this time for a different application. If the power of brain activity can be controlled by the subject's will, such modifiable signals may be used to turn on a TV set or move a computer mouse or wheelchair. Despite the poor spatial resolution of the scalp EEG, selective control of different frequencies, such the mu rhythm and its harmonics, can be exploited for differentially controlling horizontal and vertical movements of a computer screen cursor or robot arm in a two-dimensional plane (figure 8.5). In such a prototypical experiment, the subjects were asked to use whatever imagined image they could to move a cursor from the center of the screen to one of the eight possible targets at the periphery. The cursor was moved by the output of an algorithm that measured the EEG power in the 12 and 24 hertz narrow bands derived from just two electrodes over the right and left sensory-motor cortex. After a few weeks of practice, the best subjects hit the targets with high accuracy within 2–5 seconds. Besides the potential medical implications of such research for quadriplegic patients, the most striking aspect of this experiment is the selective enhancement or reduction of arbitrary brain oscillations by visual feedback. Recall that EEG is the mean field of a

22. A good progress report on the subject is Allman (1992).

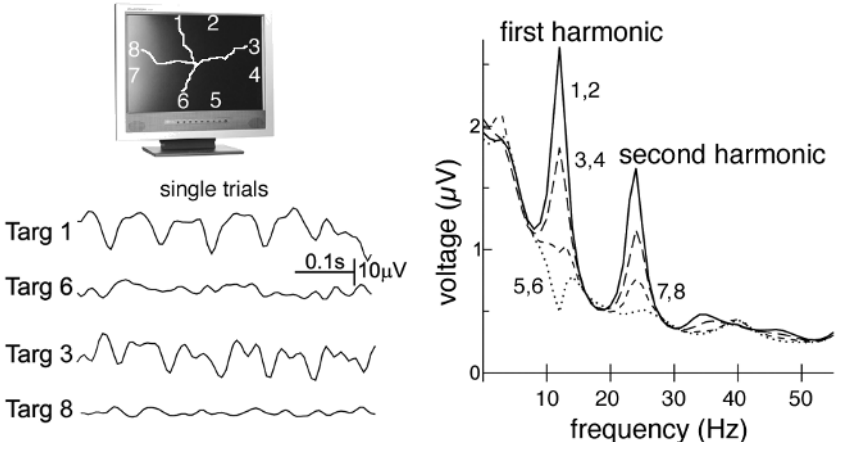

Figure 8.5. Robot control by oscillatory brain signals. The x- and y-coordinates of the computer cursor were controlled by the first and second harmonic component of the mu rhythm recorded from the subject's scalp. The subject's task was to move the cursor to one of the eight possible targets on the screen (the only feedback available). EEG traces of single trials are shown below the computer screen. Right: Average amplitude of the signal components associated with successful trials. The ability to differentially control the first and second harmonics of the field signal provides evidence that multiple generators contribute to the mu rhythm. Numbers indicate targets (as in the monitor). The 4 curves show averaged power for trials in the 4 main directions of move. Modified, with permission, from Wolpaw and McFarland (2004).

large neuronal aggregate, so it was a large collection of neurons whose coordination was enhanced by the training.[23]

Reduced Sensory Input and Oscillations

If it was simply the absence of afferent inputs that invariably give rise to the oscillations in the respective primary sensory thalamocortical areas, one might expect that occipital alpha oscillations should be particularly prominent in blind

23. The cited experiments were done by Wolpaw and McFarland (2004). Several other "brain–computer interfaces" have been used to control computers or simple robotic arms. To date, the most fascinating and creative work on the subject remains Delgado (1969). Reviews by Donoghue (2002), Nicolelis (2003), and Chapin (2004) summarize recent progress. Most current studies use surgically implanted multiple electrodes, and coordinated activity of neuronal spikes are used for instrument control, inviting serious challenges for chronic interfaces. If the goal is to control electronic devices or robots, I do not quite understand the need for such complications. A tiny magnet implanted in the tongue can generate a magnetic field large enough to be detected by multiple coils placed on the cheek or implanted in the maxilla. The virtually unlimited flexibility of tongue movement in three-dimensional space, detected by such a simple device, can do much more, much faster, and much more accurately than we can hope for from the most sophisticated brain–computer interfaces for a long time to come.

persons. This is not the case, and the underlying reason may be quite telling regarding the organization of the brain in the blind. In congenitally blind people, occipital alpha power is substantially reduced, and at the same time, alpha oscillations at more anterior normal brain sites may become more enhanced, suggesting that site-specific development of thalamocortical rhythms is under the control of appropriate sensory inputs.[24] As discussed further below, thalamocortical patterns may be critical not only for the fine-tuning of local cortical circuits but also for the establishment of long-range fibers. Both clinical experience and laboratory studies indicate that blind people are superior to sighted people in tactile processing and verbal memory.[25] Furthermore, not only do they orient themselves by sound and discriminate the changes of pitch more effectively than do healthy people, but also they may show better than average musical talent. The younger a person is when eyesight is lost, the greater these effects. "I was born with music inside me," remarks Ray Charles in his autobiography, who had lost his sight at an early age. Stevie Wonder was born blind. How does early blindness explain their exceptional musical talent?[26] The tacit implication behind this question is that if a nonallied cortical area, such as the visual cortex in the blind, is not engaged by its physiological input, it may be utilized for processing another input, provided that the long-range connections of visual areas are effectively connected to other systems. If the occipital cortex of the blind acquires newly specialized, nonvisual characteristics, it is perhaps not surprising that eye movements in blind individuals do not have a big impact on occipital alpha EEG.[27]

But what if a blind adult person regains vision? The best-known recent case is Mike May, a successful California businessman who lost his eyesight at the age of 3 and "regained" it after four decades, when a successful surgery provided him with a pristine new lens of his right eye. Despite his newly acquired vision and sensation at the level of the retina, he still travels with his dog and taps the sidewalk with a cane after 5 years of extensive visual training, although he is able to detect color and light intensity differences and can combine his extensive previous experience with his newly acquired modality. For example, from seeing a moving orange thing in the basketball court, he concludes it must be a spherical

24. Birbaumer (1970) and Noebels et al. (1978).

25. Bach-y-Rita (1972) did perhaps the most original experiments in this field by transducing optical images of a camera to an array of skin vibrators. Optical images this way produced a two-dimensional localized pattern of tactile sensations on the arm or thigh as a substitute of retinal representation. Congenitally blind people began to experience depth of objects and their position in three-dimensional space after a sufficient amount of training.

26. For the superior auditory ability of the blind, see Roder et al. (1999) and Gougoux et al. (2004). For tactile modality and verbal memory, see Sadato et al. (1996), Buchel (1998), and Amedi et al. (2003).

27. It would be important to know, though, whether tactile or acoustic stimuli can modify occipital EEG in the congenitally blind. If these functions indeed expand into the striate cortex, behavior dependence of alpha oscillations could be a way to monitor such progress. Several studies indicate visual to auditory cross-modal plasticity. E.g., spatial localization of auditory signals can activate occipital association areas that in normal persons serve dorsal-stream visual processing. For a helpful review on brain plasticity in animals and the congenitally blind, see Rauschecker (1995).

object. A brain that has been wired and trained to navigate the world through sound, touch, and smell does not easily adopt a novel sense. In fMRI experiments, presentation of faces and three-dimensional objects failed to activate his inferotemporal cortex, suggesting that such complex constellations of visual patterns have no meaning to a brain not trained to recognize such differences. On the other hand, when objects in motion were shown, high level of activity was detected in the motion-detection part of his brain.[28] Motion-detection brain areas, of course, could have been routinely activated in blind people because motion is not unique to vision. To date, no EEG studies have been performed on sight-recovery patients, so we do not know whether occipital alpha waves could eventually resume the same function as in sighted people. Nevertheless, these and related studies make it clear that anatomical wiring in early life is a critical factor in determining what kind of functions our brains can perform for the rest of our lives.

Brain in the Body: Emergence and Perturbation of the First Cortical Rhythm

Imagine that the brain and the body would mature separately in a laboratory, and only several years later we would connect them. This newly united brain–body child would not be able to walk, talk, or even scratch her nose. Local stimulation of her hand or foot would trigger generalized startle reactions, as is the case in premature babies, rather than a spatially localized motor response that characterizes a full-term baby. The reason is that the motor or sensory relations generated by the brain grown in isolation would not match.[29] In case of such mismatch, the concepts of sensation and perception will acquire no meaning. I believe that the outcome of this Frankensteinian *Gedankenexperiment* would not be much different if the eyes, ears, nose, and all sensory inputs were left connected to the brain but all effector systems were severed. The teleological argument here is that there

28. Fine et al. (2003). It is hard to adapt to a new sense:

> A Man, being born blind, and having a Globe and a Cube, nigh of the same bignes, Committed into his Hands, and being taught or Told, which is Called the Globe, and which the Cube, so as easily to distinguish them by his Touch or Feeling: Then both being taken from Him, and Laid on a Table, Let us suppose his Sight Restored to Him; Whether he Could, by his Sight, and before he touch them, know which is the Globe and which the Cube? Or Whether he Could know by his Sight, before he stretchd out his Hand, whether he Could not Reach them, tho they were Removed 20 or 1000 feet from him?

Thus wrote William Molyneux, whose wife was blind, to the philosopher John Locke more than 300 years ago (for a fascinating treatment of this topic, see Sacks, 1995). Of the dozen or so adults who learned to understand the world through their hands and ears and gained vision in adulthood, a third voluntarily reverted to the world of the blind.

29. Such disconnection of the brain from the body occurs in REM sleep. However, the brain in REM sleep has the cumulative effect of previous sensory and motor experience. Hallucinations also frequently occur during sleep paralysis, a rare condition in which a person is not able to move skeletal muscles voluntarily while awakening.

is no use in feeling or perceiving without being able to respond to the perceived stimulus one way or another.

A unique problem of somatosensation is to relate the sensory information to the real world. How do you know where your nose is without a reference coordinate system? Without an explicit reference system, it is impossible for the brain to construct reliable metric relationships among the various body parts. The brain, even if all sensors are kept intact, cannot deduce whether sensory stimuli derive from a sphere or snakelike body or any other geometry. We may suggest, then, that the basis of all spatial metrics in the brain derives from muscular action. Without the supervisor motor system, one cannot verify distance, depth, or any spatial relationship. This calibration problem is especially magnified during early development when not only the absolute body size but also relative proportions of different body parts change dramatically day by day.

How do sensory inputs affect the organization of neuronal representation of the world outside the brain, such as the body and the environment? Carla Shatz at Harvard University and Larry Katz at Duke University have demonstrated that every part of the visual system, from the retina to the visual cortical areas, does support spontaneous network patterns even if the animals are reared in complete darkness, that is, without the relevant sensory input. They hypothesized that in the presence of patterned visual inputs, the intrinsically generated connections can be modified to represent coherent patterns. Their extensive research program is summarized by the following dictum: neurons that fire together in response to external visual patterns will wire together to form functional assemblies.[30] In the thought experiment above, visual input without the ability to move can lead to modification of brain circuits, but I suspect that such altered connections have no "meaning" to the brain's owner. "Experience modifies connectivity in the developing brain" is general wisdom. But what is experience? For the discussion below, I define experience as accumulation of knowledge or skill that result from direct *action.* Implicit in this definition is that no skill or conscious (explicit) experience emerges without the brain's output. The brain can generate self-organized activity and modify its wiring according to its activity. However, without the output interacting with the body and environment, no amount of sensory stimulation can generate a useful brain.

Inspired partly by Shatz and Katz's pioneering experiments, Rustem Khazipov, Anton Sirota, Xavier Leinekugel, and I decided to search for the first self-organized pattern in the neocortex during development and examine how it is modified by the motor output generated by the spinal cord.[31] It was already known from the extensive work of our collaborator Yehezkel Ben-Ari at the Mediterranean Institute of Neurobiology, Marseille, France, that neurons in the isolated cortex of the newborn rat display "giant depolarizing potentials" due to spontaneous network excitation. Furthermore, previous work had already demonstrated unique developmental changes during the first week of life in rats, including the

30. Katz and Shatz (1996), and Feldman et al. (1999).

31. Khazipov et al. (2004).

establishment of somatotopic cortical maps, dendritic development of superficial cortical neurons, the emergence of long-range corticocortical connections, and enhanced experience-dependent plasticity.[32] How these various processes cooperate to establish the adult form of brain connectivity and behavior control, however, was not known.

Our first observation was that, in contrast to the perpetual activity of the adult neocortex, the neonatal pattern in the newborn rat pup was characterized by intermittent network bursts of neuronal activity, separated by several seconds of silent periods. The population bursts of neuronal activity were expressed in the form of a sharp potential, often followed by waxing/waning spindle-shaped field oscillations at about 10 hertz. Our intracellular recordings in anesthetized pups quickly established that the activity was a result of coordinated release of excitatory and inhibitory neurotransmitters by the already-existing local and thalamocortical inputs. Not knowing where such patterns were recorded from, most physiologists would classify these cortical field patterns as spontaneous sleep spindles or perhaps mu oscillation. Thus, we could register that the first organized pattern in the intact neocortex is a rhythm. However, in contrast to sleep spindles of the adult, the spindles in the pup were confined to a very small cortical volume. Spindles that emerged at a given spot have remained local or spread to neighboring sites at a slow speed. The explanation for such confinement of activity might be looked for at the hardware differences between the maturing and adult brains. During the first days of rat life, the cortical connectivity is exclusively local. Layer 2 and 3 neurons have very simple dendrites, and their emerging axons have yet to travel long distances. In contrast, the thalamocortical and layer 5 local wiring is already in place. The neocortex at this stage is truly locally organized, like a mosaic or a honeycomb with limited intermediate or global communication.[33] Thus, our observations in the rat pup support our previously stated claim that, without long-range cortical connections, global functional organization cannot emerge. But why does the developing thalamocortical system need a rhythm?

Rats, like most rodents, are altricial; that is, they are born with eyes and ear canals closed, rudimentary face whiskers, and poor sensory-motor coordination. Developmental biologists tell us many parallels between the first week of life in the rat and the third trimester of pregnancy in humans. Indeed, the spindles we observed in the pup are reminiscent of the brain patterns recorded from the scalp of preterm human babies, although perinatal neurologists have not yet concluded whether such patterns were signs of immaturity or part of normal development. What could be the behavioral relevance of such well-organized intermittent rhythms?

There does not seem to be much need for the body to move in the womb. Nev-

32. Ben-Ari (2005). Analogous spontaneous population patterns have been described in the neocortex by Yuste et al. (1992) and Garaschuk et al. (2000).

33. These ideas have received further support from *in vitro* work (Dupont et al., 2006; R. Cossart and Y. Ben-Ari, personal communication). Khazipov and colleagues have observed spindles in the visual area of the developing cortex, triggered by retinal waves (personal communication).

ertheless, the fetus behaves; it cannot help it. Every expectant mother becomes aware of "baby kicks" in the late stages of pregnancy. The vital importance of fetal movements is illustrated by the correlation between movement density and various postnatal fitness indices, including Apgar scores, motor and speech development, and even IQ, but the effect of these irregular, noncoordinated movements on brain development has not been addressed.[34] Analogous to human fetal movements, newborn rat pups also display muscle twitches, limb jerks, and whole-body startles, stochastic motor patterns generated by the spinal cord even in the absence of the brain. It is quite entertaining to watch the "popcorn" movements of a rat or mouse litter. After perfecting our recording system so that we could monitor brain activity in the freely behaving pup, we began to study the behavioral correlates of the earliest neocortical activity. To our astonishment, virtually all cortical spindles were associated with isolated muscle twitches, limb jerks, startle reactions, crawling, or sucking, that is, some movement. Isolated movements, such as forelimb or hindlimb jerks, triggered localized spindles in separate parts of the somatosensory cortex (figure 8.6).

Mechanical stimulation of the skin of the forelimb and hindlimb evoked the same isolated cortical responses. Our systematic comparison between the muscle activity-triggered cortical "maps" and the skin stimulation-evoked responses revealed a perfect match. Of course, neuronal activity evoked by sensory stimulation in the somatosensory cortex was not surprising and was expected from the genetically controlled primary wiring of the cortex. What was surprising was the long-lasting nature of the response in the form of spindle activity, outlasting the input by several hundred milliseconds. Let me remind the reader here that sleep spindles and the mu rhythm in the adult occur spontaneously in the absence of movement. To examine whether spindles in the newborn require an external drive or can also emerge spontaneously, we severed the lower part of the spinal cord under anesthesia and thereby prevented all sensory feedback from the hindlimbs. Despite this deafferentation procedure, spindles continued to emerge in the hindlimb area of the cortex, although at a low incidence. This latter observation provided a definite evidence for the self-generative nature of the spindle. However, in the intact developing brain, the high incidence of movement-initiated sensory feedback consistently precedes the brain-timed occurrence of spindles and acts as perturbations on the centrally generated mechanism. Again, this is in line with the laws of oscillations discussed in Cycle 5: irregular perturbations can

34. Until recently, the womb has been viewed as the romantic dwelling for the passively developing fetus, fully protected from the environment. In contrast to the subjective reports by mothers about occasional kicks, ultrasound examinations and other studies have revealed frequent motor activity of the fetus that includes twitches, random limb jerks, and rolling movements. Until the 1960s, these movements were viewed as reflex responses to some undetermined stimuli. Only after Viktor Hamburger's systematic experiments on chick embryos did it become clear that most of the early movements are self-generated spontaneous patterns (Hamburger et al., 1966). However, Hamburger's program concentrated mostly on examining and explaining how sensation can modify motor organization. For an early work on movement development, see Carlmichael (1934). For recent updates on the subjects, see reviews by Hall and Oppenheim (1987) and Robinson and Kleven (2005).

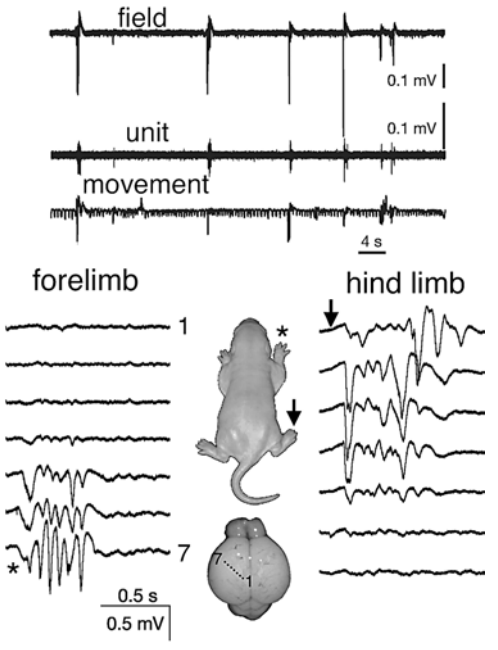

Figure 8.6. The first organized neocortical pattern is an oscillation. Upper traces: Movement-triggered spindle bursts (field and units) in a 2-day-old rat pup. Between the spindle events, no spiking activity is present. Bottom traces: Spontaneous movements of the forelimb or hindlimb trigger topographically confined spindles in the somatosensory cortex. Modified, with permission, from Khazipov et al. (2004).

trigger a premature duty cycle, provided that some sufficient time has elapsed since the preceding cycle, and reset the oscillator so that it can start charging up again. In the absence of such externally triggered synchrony, the brain provides synchrony by inducing oscillations. But what is so special about movement-triggered baby spindles?

Muscles and their tendons have sensors, which report the contractile state of the muscle to the spinal cord and eventually to the somatosensory cortex. In addition, a jerk of the extremities and muscle twitches of the tongue and face increase the chance that the skin over the muscle will touch another pup in the litter or nest material. The uncoordinated, spinal-cord–initiated muscle activity consistently activates local skin afferents with a probability proportional to the frequency of twitches in the individual muscles. Given the several hundred skeletal muscles that move the mammalian body, the number of movement combinations, in principle, may appear very high. In reality, only a limited fraction of this large combinatorial space is ever realized in motor coordination, due to the physical constraints of the bones and joints. These restrictions by the rigid body architecture and tissue elasticity reduce the extraordinarily large number of degrees of freedom that would result from the unrestrained temporal combination of sensory

inputs. Importantly, all these real-world movement combinations are meaningful inputs to the somatosensory thalamus and cortex because they will be used later in life. Using the three-dimensional physical layout of the skeletal muscles as a reference, the coordination of movement–afferent feedback–cortical spindle sequences serves to convert the initially abstract body representation in the sensory cortex to a concrete metric space. In essence, the somatosensory representation gets anchored to the real-world metric relationships of the skeletal muscles. This cannot be achieved by a general, "one-size-fits-all" blueprint since the metric relations should be customized for each body and updated as the body shape changes. In this training process, the distances between body parts are translated into a spatial-temporal organization in the somatosensory system by creating new connections and eliminating old ones by strengthening and weakening existing synaptic connections.[35]

It is important to recognize that a crude topographic map-like representation of the body surface in the somatosensory cortex does not automatically mean a functional representation. It is the synaptic connections among the neurons that provide a physiologically relevant representation. Movement-induced temporal coactivation of sensory inputs may provide the temporal tuning for synaptic connections. Because of poor axon myelination in the newborn pup, action potentials travel slowly between neurons within the brain and between the brain and spinal cord. As a result, short-lived local activity may not be sufficient to compensate for the time delays between various afferent volleys. Because spindles can sustain activity for several hundred milliseconds in somatosensory thalamocortical modules, they can serve as a temporal bridge necessary for strengthening the connections between neurons, representing different body parts. Such bridging of temporal gaps is especially critical while the motor patterns become under cortical control with the establishment of corticospinal connections and long-range corticocortical connections. These latter pathways are essential for building internal forward models that provide predictions about the sensory consequences of action.[36] Emergence of sensory-motor coordination is therefore a selection process, supervised by random muscle contractions, a competition and cooperation between movement-generated reafferentation and the self-organized dynamics of the thalamocortical system.

An important prediction of these observations is that in the absence of motor activity, somatosensory information cannot incorporate the spatial relationship among various stimuli. This likely applies to spatial relations and localization of visual and sound modalities, as well.[37] Only through movement can distances be

35. There are various ways of changing effective connectivity, including changing synaptic weights, generation and elimination of synapses, and altering ion channels. For a recent review on this topic in the developing brain, I suggest Chklovskii et al. (2004).

36. I refer here to the intracortical substrate of the hypothesized *reafferenz prinzip* or corollary discharge (von Holst and Mittelstaedt, 1950; Sperry, 1950).

37. Although not emphasized by the authors, spindlelike oscillatory patterns are also present in the visual cortex of the developing ferrets, and they can be triggered by visual stimuli (Chiu and Weliky, 2001).

measured and incorporated into our sensory scheme. For an immobile observer, direction, distance, and location of sensory information are incomprehensible and meaningless concepts. The real test of this hypothesis would require paralyzing the skeletal muscle system during the early maturational stage of the brain, before the appearance of sensory-evoked spindles. Although no such experiment has been performed, the available data are in support of such a scenario. Cutting the facial nerve selectively abolishes whisker movements without directly affecting sensory innervation of the facial vibrissae, the tactile organs used by rats to discriminate object shape and texture. If selective paralysis of whisker muscles by severing the facial nerve is carried out during the second week of life, whisker representation in the thalamus is severely reduced and disorganized, even though whiskers can still be actively used by the head and body turns. Touching the whiskers will still evoke responses in thalamic neurons, but their directional organization is missing in these animals, supporting the idea that movement-induced sensation is the basis of representation in the physical world. A related experiment examined the consequences of early limb immobilization on subsequent development of walking. In the rat, the adult pattern around locomotion emerges about the 15th postnatal day. Immobilization of one hindlimb in an extended position by a cast around the leg for the first 3 weeks of life resulted in long-lasting abnormalities in the timing of the electromyographic activation patterns of the immobilized muscles, although the rats eventually acquired adult walking patterns. This procedure, of course, did not prevent muscles from twitching and associated sensory reafferentation from the hindlimbs even in the presence of the cast. The importance of action on perception is also obvious in the adult. When all spinal tracts are cut except for the lemniscal system, which carries the topographical representation of the body surface from the spinal cord to the thalamus, one may expect that sensation below the cut should remain intact because the major sensory conduit from the body to brain is still intact. Nevertheless, experimental rats tend to ignore stimulation below the cut.[38]

Ultrasonic images of human fetuses often document them sucking on their thumb. According to our observations in the rat pup, such motor patterns trigger temporally coordinated spindles in the mouth and tongue representation of the cortex. John Allman at the California Institute of Technology, Pasadena speculates that if the fetus consistently sucked on the thumb of one hand as opposed to the other, the increased stimulation might favor the development of its cortical representation, which in turn might lead to hand preference and asymmetry of cerebral representation.[39]

38. Wall (1987). The lemniscus medialis is a fiber tract originating from the gracile and cuneate nuclei and decussating in the lower medulla before terminating in the ventral posterior nucleus of the thalamus. It conveys somatic-sensory information involved in tactile discrimination, position sense, and vibration sense in a somatotopic manner.

39. Nicolelis et al. (1996), Westerga and Gramsbergen (1993), and Allman (1999). The research program of Potter et al. (2006) tests these ideas by connecting output patterns of neuron cultures to robots and using the outputs of the robots' sensors to modify neuronal connections.

The primacy of movement-induced sensory feedback may also underlie more complex processes such as development of social communication and speech. Songbirds, such as the extensively studied zebra finches, learn their songs from their fathers. This process is more serendipitous, though, than a well-thought-out learning algorithm. The young birds do not start with the first syllables of the father's song and acquire the rest piece by piece. Instead, each bird "babbles" some sounds, and it is these self-generated "syllables" from which the birds expand to learn a species-specific adult song. Each bird starts out with a unique seed syllable. Analogously, babbling in human babies also reflects a self-organized intrinsic dynamics. When the uttered sounds resemble a particular word in a given language, parents exploit the internal dynamics of the brain by reinforcing the spontaneous utterances. As I have stressed all along, perturbation of the default self-organized patterns of the brain is a more effective mechanism of pattern formation than the de novo, *tabula rasa* approach because the former can exploit the existing dynamics of the maturing brain networks.[40] The brain, body, and the environment are highly intertwined systems at multiple levels, and the "upward causation" of somatic, humoral, autonomic, and environmental processes and their dynamical interactions is as important as the "downward" causation of the brain on their effectors (recall figure 2.1).[41]

Following axon myelination, the connection speed between assemblies and regions becomes faster and spindle-mediated prolongation of sensory feedback activity is no longer needed. Parallel with the establishment of sensory-motor coordination, the thalamocortical circuit becomes under the control of subcortical modulatory systems, which prevents the occurrence of spindles in the adult waking brain. Early development is thus a "wakening" process of the forebrain from its dominantly sleeplike state. Nevertheless, spindles continue to emerge during early stages of sleep throughout life. As discussed in Cycle 7, sleep is generally viewed as the brain's separation from the environment and, to a large extent, from the body. Nevertheless, at least a portion of spindles are triggered by movement-initiated afferent activity, similar to the developing brain. Occasionally, we all experience spontaneous muscle twitches or even large startle motor patterns that seize our whole body at the transition to sleep.[42] Such movement-initiated afferent excitation

40. The zebra finch work is cited from Goldstein et al. (2003). Ontogeny of phonetic gestures is discussed in Vihmam (1991) and Kelso (1995). Sporns and Edelman (1993) suggest that movement coordination is also an issue of selection from large battery of primary movement repertoire.

41. The "situatedness" or "embeddedness" of the brain in the body and environment is discussed in detail in Varela et al. (1991). Several other excellent works have dealt with the "reciprocal causality" issues of the brain–body–environment continuum (Changeux, 1985; Chiel and Beer, 1997; Panksepp, 1998; Damasio, 1999; O'Regan and Noe, 2001; Thompson and Varela, 2001). For computational aspects of similar issues, see also Salinas and Abbott (1995).

42. Young kids and teenagers often have difficulty sitting quietly and feel a strong urge to move their legs. In 2–3% of the population, that feeling may be impossible to resist, and this minority is diagnosed with periodic limb movement disorder (PLMD) or restless legs syndrome (RLS), distinct but related disorders (Wetter and Pollmacher, 1997; Glasauer, 2001; Odin et al., 2002; Hening, 2004). Although other extremities may also be affected, movement of the legs is more typical and occurs mainly during rest or light sleep, causing insomnia. Muscle jerks typically occur for 0.5–10 seconds, at intervals separated by

can trigger K-complexes followed by sleep spindles. One can only speculate that the function of sleep spindles in the adult is therefore not fundamentally different from that of the early cortical spindles. The shape and size of the body change not only during early development but also throughout the life span. If sleep spindles or mu oscillations are indeed analogous to the baby spindles, these rhythms engaging the somatosensory system may assist in the preservation of body representation.

The action strategy used by the developing brain is retained in adulthood, as demonstrated by the extensive work of Nikos Logothetis and colleagues at the Max Planck Institute in Tübingen, Germany. These investigators study the neuronal mechanisms involved in binocular rivalry, when the visual system is confronted by an ambiguous figure (figure 8.7). Their consistent finding is that the activity of neurons in visual cortical areas alone cannot determine the perceptual changes underlying the brain's verdict. A critical element in this process, they believe, is the object's continual surveillance by eye movements. Seeing is an active exploration of the environment.[43]

The primacy of movement in the visual domain is also well illustrated by the classic experiments in kitten pairs performed by Richard Held and Alan Hein at Brandeis University in Waltham, Massachusetts. One of the pair was wearing a harness and could move around freely in a circular track, while the experimental kitten was strapped in a suspended gondola, which was pulled by the free cat. Outside the experiments, the kittens were kept in darkness. After several weeks of training, the cats were tested for sensory-motor coordination. As expected, the free cat behaved just like any other ordinary cat. Its yoked partner, on the other hand, did not stretch out its paws when lowered to the ground, often bumped into objects, and could not coordinate its movements properly with visual objects because motor behavior was not in register with visual input. Held and Hein concluded that perception is learned through the action of the motor system.[44] Perception is not simply a feedforward process of sensory inputs but rather is an interaction between exploratory/motor-output–dependent activity and the sensory stream. It is something we *do*. To conclude this Cycle, I paraphrase Theodosius Dobzhansky (Cycle 3 epigraph) by stating that nothing in the brain makes sense except in the light of behavior.

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5 to 30–90 seconds. These disorders may reflect a developmental problem of the brain and spinal cord, a persistence or reemergence of the physiological fetal movement patterns. Notably, periodic limb movements often trigger K-complexes (Mello et al., 1997).

43. See Leopold and Logothetis (1996, 1999) and Sheliga et al. (1994). The critical role of eye movements in visual perception is also emphasized by Mriganka Sur and colleagues (Sharma et al., 2003). The observation that "neglect," a difficulty in acknowledging the affected part of the visual field even if it represents part of one's own body (Kinsbourne, 1987), arises from damage to parietal cortical areas serving motor activity further underlies the primacy of motor activity in sensation (Rizzolatti et al., 1983). For philosophical implications of the effect of movement on perception, see O'Regan and Noe (2001).

44. Although Held and Hein (1963) emphasized the role of active exploration, they attributed the observed effects to extensive visual experience, rather than to the primacy of motion in providing the necessary real-world metric for depth perception.

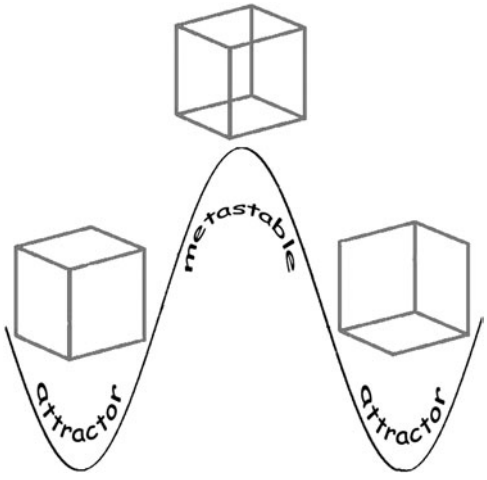

Figure 8.7. Metastability of ambiguous figures. Ambiguous figures, such as the Necker cube, are perceived as one of several possible stable configurations (e.g., the box here is either seen from the top or the bottom). These perceptual shifts are initiated by eye movements.

Briefly . . .

Sleep is the default state of the brain—default in the sense that it develops as a self-organized or spontaneous state without an external supervisor. Sleep shares numerous features with autonomous early brain development. Both are not homogeneous states but evolutions of "stages" in which oscillations temporarily stabilize brain dynamics. The neurons' spiking content of these stages should be predictable from the initiating conditions owing to the deterministic nature of oscillations. Perturbation of the spiking patterns by events that occur during a waking experience may change the initiating conditions and, therefore, the content of spiking patterns during sleep and early development. It has been conjectured for more than a century that sleep may serve to cement or consolidate memories by replaying parts and details of the waking experience. Initially, this service of sleep was contributed exclusively to REM sleep and its dream content. Recent experiments stress the primary importance of slow-wave sleep and other "off-line" states in the consolidation process because their population dynamics share several similarities with conditions that favor synaptic plasticity. Human studies consistently show that sleep leads to a gain in memory and skill performance when compared to the same amount of waking time passed. Extensive or life-long stereotypic experience, such as meditation, athletic, and other skills can lead to quantitatively measurable alternation of oscillatory patterns in the relevant cortical representations.

Without supervised training, the brain does not develop a sense of real-world relationships. There is no a priori reason why representation of the environment

in the brain should be three-dimensional and linear, instead of *n*-dimensional and logarithmic or exponential. The brain's sensory representations acquire real-world metrics early in development. A key mechanism in this supervised training is the muscle-activity–generated sensations, which begin during late intrauterine life. It is the three-dimensional layout of the skeletal muscle system that provides the real-world metric to the sensorium by triggering oscillations in the thalamocortical system at critical times of brain development that coincide with the emergence of long-range corticocortical and corticospinal connections. Without the supervision of the muscular system, the brain has no sense about the shape of the body. Similarly, brain-controlled action is likely necessary for other perceptual skills, such as vision and spatial orientation.

Until recently, exploring the complex mechanisms of rhythms in the resting-sleeping brain was not a high priority because it was not clear whether they serve some important functions or are merely epiphenomena. The reasons outlined in this Cycle, however, justify the need for extensive explorations. The significance of these oscillations does not really begin to become apparent until their content is uncovered and related to waking behavior. This endeavor will require large-scale recording of neuronal spikes in behaving animals.

Cycle 9

The Gamma Buzz: Gluing by Oscillations in the Waking Brain

> This . . . obliged us to abandon, on the plane of atomic magnitudes, a causal description of nature in the ordinary space-time system, and in its place to set up invisible fields of probability in multidimensional spaces.
>
> —Carl Jung, *On the Nature of the Psyche*

Systems neuroscience was at its deep point in the 1980s, and several factors contributed to its depression. Among the reasons were the radical innovations in single-cell-level biophysics with the introduction of the *in vitro* slice preparation and the rapid spread of molecular biological methods, followed by the invention of functional imaging of the intact human brain in the early 1990s. While these novel innovative methods provided new windows into the brain, systems neurophysiology stagnated with its classic theories and methods of single-cell recording. Systems neuroscience transiently lost its ground and many of its followers. This situation was instantaneously and radically changed by a historical event, the symposium on visual perception at the Society for Neuroscience meeting in Washington, DC, in the fall of 1993. I have never seen so many neuroscientists attending any lecture on any topic of neuroscience than at that milestone event. The giant auditorium was unbelievably packed, and many could not get in. Obviously, the interested audience came from all walks of life and represented neuroscientists from the molecular to cognitive levels, with only a small fraction of the attendants working directly on the problem of vision perception. The unprecedented attendance was an overt declaration that complex structure–function issues of the brain fascinate all neuroscientists.

After a long vacuum in systems research, a radically different and comprehensive theory was on the horizon. The protagonist of the symposium was Wolf Singer from the Max-Planck Institute in Frankfurt-am-Main, Germany. The respondents

were equally experienced and equally wise experts. The essence of Singer's message was this: representation of the various attributes of the visual world by distributed neuronal assemblies can be bound together harmoniously in the time domain through oscillatory synchrony. The "binding by synchrony" proposal, the shorthand term of the theory, was a paradigm shift in the structure–function relationship of the nervous system because, according to the theory, it is no longer the connectivity per se but the coherent temporal organization of activity through oscillatory synchrony that matters. Although many objections and alternative mechanisms have been raised at that meeting and afterward, the temporal binding hypothesis of object perception has remained the most debated framework to date.[1] What really clashed at that symposium and what makes the continued dispute all the more interesting is the relationship between space and time management in the brain.

Binding by Bottom-Up Connectivity

What is the figure and what is the background in a Vasarely painting? Is the spotted salamander part of the leafy ground or separate? How does the visual system make a distinct decision in each case? According to Béla Julesz, what makes an object an object and a figure a figure is the temporal and/or spatial coherence of the parts. The camouflage effect of the salamander's skin is effective only as long as it remains motionless. Movement of parts or the whole of its body makes it clearly detached from the background of otherwise statistically identical features. Features that move together tend to belong together: they have a common fate, as Gestalt psychology has stated long decades ago. However, not all attributes of an object are always present all the time, and recognition of an object depends on successful completion of the pattern on the basis of past experience. Dogs have characteristic size, shape, color, odor, fur texture, and walking and barking patterns that distinguish them from other animals. Proper combination of these features should be bound together into a single image in the brain to recognize a dog or an individual dog even if the size, viewing position, and lighting conditions change. Because these features are processed in separate parts of the cortex by different sets of neurons, one should explain how they are bound into a complex representation in a matter of 200 milliseconds or so. This is called the binding problem.[2] A related problem is to avoid "superimposition" of coexisting patterns,

1. The journal *Neuron* has dedicated an issue to the binding problem, with excellent reviews presenting both the advantages and shortcomings of the theory (Roskies, 1999). See also Phillips and Singer (1997).

2. Of course, binding is not a problem for the brain. The problem is to understand the mechanisms by which the brain achieves it. For discussions of the "binding problem" and feature extraction, see Zeki and Shipp (1988), Damasio (1989), Singer (2001), Varela et al. (2001), Engel et al. (2001), Engel and Singer (2001), and Mesulam (1998). The speed of visual processing in humans has been measured by Thorpe et al. (1996) in a simple go/no-go categorization task (whether the picture contains an animal or not). However, no first-time viewer can extract a Dalmatian dog from a background of black and white patches or find Carmen San Diego in the busy scene of Fishermen's Wharf in such a short time.

such as the motionless spotty salamander and the leafy background, and separate them into distinct entities. The problem of binding and superimposition invokes the already familiar problem of the delicate relationship between integration and segregation and the logical constructs of similar and different. The neurophysiological essence of the problem is how neurons activated by the shape, color, motion, and other attributes of the salamander and the leafy background give rise to one or two representations.

The first neurophysiological explanation to the binding problem was provided by David Hubel and Torsten Wiesel then at Harvard Medical School, Boston. In their recordings in anesthetized cats and monkeys, they found that most neurons in the primary visual cortex (V1) discharge only in a restricted part of the visual field with a phase-dependent fashion to a moving bar. They called these cells "simple" cells. Another class of neurons, called "complex cells," had bigger receptive fields and showed no phase dependence. They suggested that multiple simple cells converge onto complex cells, and the integration of smaller receptive fields by the complex cells makes the latter cell type respond to stimuli in a larger area of the visual field. Some neurons in visual areas downstream to V1 responded to higher order features of the stimulus (e.g., edges), which are called "hypercomplex" cells. The straightforward and admittedly simplified conclusion of these observations was that the visual system is a feedforward, hierarchical processing system representing at each step more and more complex features of the input, in line with the prevalent "input–decision–output" serial processing theories of brain function.[3]

Numerous findings from various disciplines of neuroscience provide support to this feedforward model. The visual cortex in primates is organized into a collection of anatomically distinct areas with a gradual decrease of the foveal dominance of retinotopic specificity.[4] At each stage of visual processing, neurons respond to somewhat distinct attributes of the visual input, indicating physiological specialization of subsequent stages. Neurons in subsequent stages combine features of inputs from earlier stages, losing first-order features and gaining more complex, higher order features. Importantly, separate streams of structures in the primate parietal and inferotemporal cortical areas appear to funnel fundamentally different aspects of visuals scenes.[5] The ever-increasing combinatorial complexity, a result from the ascending hierarchy of neuronal

3. The sensory input–decision–response model is not unique to the visual system and has been the dominant framework in all systems. It is a direct descendant of the sensory input–response models of psychology (often referred to as the Hull-Spence theory; Pavlov, 1927; Hull, 1952; Spence, 1956), and its origin can be traced back to the British empiricists.

4. Retinotopy is the maplike correspondence between receptor cells in the retina and the surface of the visual cortex of the brain. The map is highly nonlinear in a sense that the fovea is disproportionately represented in V1 but the representations of foveal and extrafoveal areas tend to equalize in higher order visual areas.

5. Felleman and Van Essen (1991). The dorsal and ventral streams of visual structures have been suggested to segregate spatial localization ("where") and recognition ("what") of objects (Ungerleider and Mishkin, 1982). Goodale and Milner (1992) argue that "vision-for-action" and "vision-for-perception"

computation, culminates in unique neuronal patterns of the inferotemporal cortex. Several neurons in this region were found to fire selectively to hands, faces, and other discerning features. The key property of these cells is their context, scale, and translational invariance, that is, the persistent selective firing in response to the same object even when the background, size, or position of the object varies in the visual field. They *explicitly* represent the common features of the object.[6]

Neurons with complex synthetic properties have been long hypothesized to exits. The Polish behavioral scientist Jerzy Konorski was the first to suggest that performance depends on highly specialized "gnostic units."[7] Subsequently, the British neurophysiologist Horace Barlow estimated that a small population, perhaps a few hundred to a thousand, gnostic or "cardinal" neurons was needed to give rise to a percept.[8] These considerations also provided a long-standing strategy for neurophysiological research, Barlow's "single-cell doctrine," which claims that by recording neurons one by one in subsequent stages of processing, one can infer all computations of the brain about an object as long as physical features of the object remain unchanged during the recording.[9] According to this signal processor model, lower level features of an object are represented in early stages of a feedforward system, and the features become progressively more complex as lower level information is combined. Barlow writes:

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distinction is more appropriate. E.g., the middle temporal visual area (MT) and V4 belong to the ventral and dorsal streams, respectively, and show selectivity for direction of motion (MT) and selectivity for color (V4) (Van Essen and Zeki, 1978; see also Felleman and Van Essen, 1987). Nevertheless, the dorsal and ventral streams have many anatomical links, and there is considerable intermixing of the signals and representations (Ghose and Maunsell, 1999). Importantly, it is not clear how perception can exist without action.

6. Face, hand, and banana-specific neurons were described by Gross et al. (1969; see also Desimone et al., 1984; reviewed in Gross, 1992; 2002). Unfortunately, *in vivo* neocortical physiology rarely identifies the recorded neurons. Therefore, the anatomical identity of higher order, gnostic neurons (see note 7) to date has remained unknown.

7. Konorski (1967) is an excellent summary of instrumental conditioning from a unique Eastern European perspective. Konorski was a student of Ivan Petrovich Pavlov but was strongly influenced by American behaviorism. His "gnostic neurons" were essentially decision makers between the input and action.

8. Barlow referred to such highly complex cells as "cardinal" cells (Barlow, 1972), implying that various aspects of an object (e.g., your grandmother) and constellations of the lower level features converge to represent increasing orders of features in a feedforward hierarchy. It is not clear, though, how Barlow estimated the necessary number of neuron for perception. Abbott et al. (1996) estimate that 25 temporal lobe neurons can identify as many as 3,000 faces as familiar or unfamiliar. Similarly, Shadlen et al. (1996) suggest that approximately 100 neurons are sufficient to signal the direction of moving clouds of dots. These estimations assume that neurons "code" as independent units, an assumption that may not be granted in interconnected networks.

9. The statistical argument in favor of the single-cell doctrine is this: large numbers of sequential responses of a single neuron converge to a histogram of the same shape as does the response of a large ensemble of identical cells to a single stimulus, as predicted by the central limit theorem. This statement, however, is true only if the brain state remains stationary during the entire time between stimulus presentations and if the previous signals do not affect subsequent ones. However, such stationarity conditions are hardly ever satisfied in the brain (Martin, 1994).

> Our perceptions are caused by the activity of a rather small number of neurons selected from a very large population of predominantly silent cells. The activity of each single cell is thus an important perceptual event and it is thought to be related quite simply to our subjective experience. The subtlety and sensitivity of perception result from the mechanisms determining when a single cell becomes active, rather than from complex combinatorial rules of usage of nerve cells.[10]

In his view, activity of a special group of small cells is responsible for even the most complex brain activity.

The unidirectional feedforward system eventually should converge on the top where gnostic units will bind all critical features and therefore explicitly represent the object. In further support of the convergence theory, virtually any arbitrary complex feature of an object, such as a particular orientation of a bent paperclip, can be extracted from the firing patterns of inferotemporal neurons in a monkey. However, such ability does not come free and subtle discriminations in any modality require months and years of training.[11] The final, and perhaps strongest, backing of the theory is the relationship between the gnostic units and behavioral performance. Experimenters have repeatedly reported on neurons in visual and other cortical areas where firing patterns of single neurons reliably predict the behavioral outcome of the animal, even when its decisions are based on ambiguous stimuli.[12] Binding solved.

Yet, a purely feedforward model with its feudalistic hierarchy just cannot be the whole story. First, and most important, it does not assign a role to the equally extensive feedback connections in the cortex.[13] A physiological theory that leaves out half of the anatomical connections cannot be complete. A second frequently

10. Barlow (1972, p. 372).

11. Experiments with paperclips were done by Logothetis and Pauls (1995; see also Logothetis, 1998). For a summary of the firing patterns of inferotemporal neurons, see Tanaka (1996). In the neuronal network literature, high-order representation of information is referred to as "sparse" coding (an idea equivalent to "gnostic" or cardinal cells but without subjective connotations). Perhaps the greatest appeal of sparse coding is its energy efficiency (Levy and Baxter, 1996; Laughlin and Sejnowski, 2004). Highly sparse coding has been characterized in several systems, including the hippocampus (O'Keefe and Dostrovsky, 1971), the Kenyon cells of the olfactory system in insects (Laurent, 2002), and in the song-generating system of zebra finches (Hahnloser et al., 2002).

12. An informative review on the match between unit firing patterns and behavioral performance is Parker and Newsome (1998). For an early overview, see Perrett et al. (1984). Note, though, that a match between performance and unit firing does not mean that the recorded units are responsible or critical for the behavior. Stimuli can evoke similar patterns under anesthesia or sleep in the absence of a behavioral output. Just because behavior or stimulus occurrence can be deduced from the spike patterns by the experimenter does not mean that the same format is used by the downstream neurons for "reconstructing" the stimulus or executing an output pattern.

13. Axon terminals from the thalamic lateral geniculate account for no more than 5 percent of the total synapses in V1. Consequently, 95 percent of the excitatory synapses, even in V1, are supplied by local neurons and neurons of other cortical areas and other thalamic nuclei. Similarly, the feedforward projection from V1 to MT provides fewer than 5 percent of the excitatory synapses from V1. In fact, a large portion of inputs come from nonvisual areas. Local computation will hence be markedly affected

used reasoning against the hierarchical model of visual recognition is the "combinatorial explosion" problem.[14] The argument goes like this: if at least one gnostic cell is required to represent each possible combination of 100 hundred shapes, 100 positions, and 100 colors, then 1,000,000 neurons would be needed to represent all possible combinations. Of course, if one keeps adding other features, the numbers rise quickly. Because the number of neurons needed grows exponentially with the number of unique objects represented by their numerous features, the brain, so the story goes, quickly runs out of neurons. The situation is much worse, of course, if instead of single cells, populations of cells are taken to represent individual features. However, this purely mathematical argument may not hold in the brain. It is hard to estimate the number of unique objects the human brain can recognize, but it is surely not a galactic number. Most of us, non-Eskimos, cannot discriminate hundreds of shades of white, and an average person can name no more than a dozen geometric shapes. On the brain side of the equation, neurons are not independent coding units but are parts of a strongly interconnected system. This interconnectedness puts a clear limit on our ability to discriminate among unfamiliar objects. What I judge as similar may be judged as dramatically different by someone else with a different perspective.[15] Nevertheless, I do not see how the combinatorial explosion argument can be justified without a proper estimation of the number of objects a brain can recognize.

The third objection concerns the exact location and spatial relationship of the gnostic neurons. Are they clustered in a small volume, such as a cortical column, or are they distributed over a large area? Clustering of gnostic units does not appear to be the case. Clustering invites vulnerability to attacking agents. Devastating ailments, such as Alzheimer's disease, are characterized by myriads of localized attacks on cortical columns.[16] However, the random damage of cortical columns never results in the inability to recognize a particular book, a finger, or a specific family member. Instead, the patients lose the combinatorial mechanisms needed for recognition. On the other hand, if the postulated gnostic units are distributed, we face a fundamental problem: how do the gnostic units communicate, and where do they send their messages? This would require special wiring, which would make gnostic units special not only because of their conjunction-specific response properties but also because of their highly specialized wiring. The complex features represented by gnostic neurons may derive not from their special

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by information arriving from a very wide variety of sources. The architecture is thus rather inconsistent with a strict feedforward analysis and implies that vision is more an inference than a hierarchical analysis (Young and Scannell, 2000). Douglas et al. (1995) discusses the numerous advantages of recurrent neocortical circuits.

14. Von der Malsburg (1985).

15. Goldstone (1998) discusses the literature on the ability of trained observers to recognize orders of magnitude more features than untrained subjects. The ability to match or detect differences between colors, including shades of color and brightness, varies considerably among the normal population. One out of 20 humans does not have normal color vision (Goldstein, 2002).

16. For the neuronal loss pattern in Alzheimer's disease, see Terry et al. (1991). Multi-infarct dementia is another condition where multiple "random" damage occurs but mostly in the white matter.

morphology or intrinsic biophysical features but from their functional connectivity and the dynamics of the network in which they are embedded.[17] If all currently active neurons to a particular face were selectively and instantaneously eliminated in the inferotemporal cortex in my brain, I would not suffer from face recognition problems because neighboring neurons would instantaneously take over the response properties of the eliminated cells.[18] Another objection that can be added to the list of criticisms is that purely feedforward circuits with closed ends do not really exist in the brain. There is no top in the brain hierarchy and the bottom-up paths are always coupled to top-down connections. So the gnostic neurons would inevitably end up sending their impulses back to earlier processing stages.

But what is the point of sending impulses back to neurons representing the elements of an object after the whole has been already identified by the gnostic units? Because there are no stop signals in the bottom-up model, it is not clear what mechanisms would prevent the reverberation of activity in an interconnected system after an object is recognized. The hierarchical feedforward model lacks a temporal scale that would ensure the discrete and timely transfer of information from one stage to the next. In the absence of such a timing mechanism, it is not clear how the input can be effectively linked to the output and become useful in the real world. Oscillations, as discussed in Cycle 5, are perfectly suited for such temporal segmentation. The existence of rhythms in the visual system, such as the prominent alpha waves, is the physiological telltale sign of excitatory feedback loops in action. Last but not least, the feedforward model is essentially a sequential integrator and has limited options to compare a newly created representation with all the semantic knowledge stored about related images.

The purely hierarchic mode of operation is equally problematic in the effector systems of the brain. Even if we identify a mechanism for flexibly connecting the postulated gnostic units at the perceptual end, it remains to be explained how the action system of the brain can be mobilized effectively by a handful of decision-making neurons at the top of an inverted hierarchy and how it can break down the tasks efficiently into subroutines for motor and other outputs. The bottleneck problem of highly convergent sensory inputs and extensive divergent outputs assumes a central command that, when damaged, should result in simultaneous impairment of perception and voluntary motor execution. Clinical observations and experimental lesion studies do not support such a scheme.

As a final point, there is an important philosophical objection. The very notion of the hierarchical model assumes that what we *see* is already present in the two-dimensional image of the retina and that the physiological process of seeing is a

17. I discuss how explicit representation may emerge from functional connectivity in Cycle 11.

18. This claim, to date, has no experimental support but follows from the dynamic organization of cortical networks. My claim is, of course, very different from the condition known as prosopagnosia, which is an impairment of face recognition that arises from a damage or developmental problem of a circuit. For a patient-described lucid introduction to this condition, visit Cecilia Burman's website at http://www.prosopagnosia.com.

sequential extraction of information, which is already present at the level of the input. The strictly feedforward model of sensory processing does not allow combination the currently sensed inputs with past experience. Because of unidirectional flow of information, feedforward architectures cannot learn with network growth. Bootstrapping into higher order requires networks with emergent properties. Systems with emergent features require feedback. Since feedback loops are available, they are likely to be very important in processing sensory information or combining the sensory inputs with past experience.

Binding by Time in a Decentralized Egalitarian Brain

An alternative to the hierarchical connectionist model of object recognition is a more egalitarian solution: binding by temporal coherence. The key idea of this model, usually attributed to Peter Milner, a colleague of Donald Hebb at McGill University in Montreal, and to the German theoretical physicist Christoph von der Malsburg at the University of Heildelberg, Germany, is that spatially distributed cell groups should synchronize their responses when activated by a single object.[19] In this new scheme, connectivity is no longer the main variable; rather, it is the temporal synchrony of neurons, representing the various attributes of the object, that matters. The different stimulus features, embedded in the activity of distributed cell assemblies, can be combined by mutual horizontal links.

Perhaps the most fundamental difference between the feedforward hierarchical and temporal synchrony models is that a causal (i.e., temporal; see Cycle 1) sequence of events is required for the hierarchical model, whereas events occur simultaneously without causal features between the different attributes and higher order features in the synchrony model. The roots of the ideas behind the temporal binding model can be traced back to the notion of "synchronicity," coined by Carl Gustav Jung and Wolfgang Pauli. After his mother's suicide in 1927, a failed brief marriage to a cabaret dancer, and being routinely thrown out from every café in town for drunken behavior, Wolfgang Pauli fell into a deep, personal crisis and consulted the already famous psychoanalyst Carl Jung. Their relationship began as a 2-year phase of doctor–patient connection, but their dialogue continued for many years at a higher intellectual level. As a physicist, Pauli searched for a unified field theory, whereas Carl Jung was looking for a unifying principle behind meaningful coincidence, individual consciousness, and the totality of space and time. The concept of "synchronicity" was born from reviewing more than 400 of Pauli's dreams. After several years of discussion, they defined synchronicity as "the coincidence in time of two or more causally unrelated events which have the same or similar meaning." Synchronicity describes some striking and apparently inexplicable "meaningful coincidences" or "significantly related patterns of chance" when, for example, the contents of a dream are paralleled in a pattern of

19. Milner (1974) and von der Malsburg (1985, 1999).

seemingly unconnected external events. In their use of the term, synchronicity corresponds to an "an acausal connecting principle," as apposed to causality (see Cycle 1), which is "the modern prejudice of the West."[20] Perhaps realizing the difficulty in separating synchronicity from chance coincidence, Pauli later preferred to speak of meaningful correspondences (*Sinnkorrespondenzen*) or holistic order (*ganzheitliche Anordnung*).[21]

The most attractive feature of the egalitarian binding by synchrony hypothesis is that, in principle, it offers a virtually endless coding capacity for feature combinations. In addition, cross-modality representations can be mapped directly onto each other, using the same format. There is only one catch. Flexible representations of *any* feature that might coexist with any other feature would require inexhaustible lateral connections, including long-range wiring between modalities and sensory-motor domains. Laying down cables for extensive distant connections requires more space and is much more expensive to maintain than is multiplying neurons with local connections. The small-world-like architecture of the neocortex with its limited density of long-range connections does not quite meet this requirement.[22] This is where oscillation as a linking mechanism comes handy, since synchronization by oscillation is effective even through a few and weak links (Cycle 6). During the oscillation, alternating cell assemblies can synchronize in subsequent cycles, providing a time-multiplexing mechanism for the disambiguation of superimposed images or figure versus background separation. A particular assembly can be defined by a short or single barrage of synchronous spikes, whereby each individual neuron needs to contribute only a single or few spikes. Such self-organized, synchronous coalitions can be established very rapidly.[23]

20. Pauli was never formally Jung's patient, and the doctor–patient relationship was mainly confined to analysis of Pauli's dreams. Their joint book (Jung and Pauli, 1954) is a result of many years of discussion. However, the real flavor of the debate between these two intellectual giants, arguing from different sides to find mutual enlightenment, is better documented by their long exchange of letters from 1932 to 1958, published first in German in 1992 and translated recently into English (Meier, 2001). The phrase "acausal connecting principle" reflects Jung's struggle with the Aristotelian logic and deduction. Emergence and circular causation as explanations arrived many years after Jung and Pauli thought about these issues.

21. Pauli described his uncertainty in an essay, "The Piano Lesson" (*Die Klavierstunde*), written to the psychologist Marie-Louise von Franz. In it, he described how an exotic Chinese woman appeared to him in his dream as a piano teacher before he had to give a lecture about the union of matter and psyche. The "real" content of this letter is Pauli's hesitation about issues of synchronicity versus coincidence as scientifically verifiable entities (see Bennet, 1985). Pauli's suggestion was to detach the psyche of an observer from any observed phenomenon. In contrast, Jung insisted that the observer's psyche is implicitly part of the experimental setup, results, and interpretation. David Peat's book on synchronicity (Peat, 1987) discusses further the liaison between psychology and physics and attempts to find a connection between quantum theory and synchronicity and, in a broader context, between matter and mind.

22. As discussed in Cycle 2, it does not have to, because the world is highly constrained, and associations are not entirely unlimited in scope but determined by the statistical features of the environment.

23. For rapid self-organization of population events, see Buzsáki et al. (1992).

How does all this theoretical reasoning translate into neuronal mechanisms? The first round of experimental support for the temporal synchrony conjecture was provided by Singer and Charles Gray, then a postdoctoral fellow in the Singer laboratory.[24] Departing from the tradition of single-unit recording and analysis in sensory systems, they recorded not only multiple-unit activity but also local field potentials from single electrodes placed in the striate cortex (V1) of anesthetized and paralyzed cats. Using simple correlational analyses of unit firing and Fourier spectral methods, they discovered that a significant fraction of the recorded signals displayed oscillation in the 30–60 cycles per second (i.e., gamma-frequency) band in response to moving bars. These gamma "bursts" of field and multiple-unit oscillations, lasting from tens to thousands of milliseconds, were rarely observed spontaneously but were reliably induced by visual stimuli. Optimal stimuli that induced the most robust unit discharge produced the largest amplitude field response, whereas suboptimal stimuli evoked less unit discharges and less regular field oscillations. Unit activity was phase-locked to the trough of the field oscillation, but neither the units nor the field showed any evidence of being time-locked to the onset or other aspects of the visual stimuli (figure 9.1). These findings provided conclusive evidence that the oscillatory ensemble events emerged locally. The oscillatory dynamics were not directly related to the stimulus but were added on by the brain. Gamma oscillation in the activated neocortex finally found a putative function 50 years after its discovery.[25]

These initial observations have given rise to a barrage of experiments in various systems and species. Perhaps the most important observation is that synchrony between various locations occurs only when neurons at those locations respond to related visual features of the object. Neurons with overlapping receptive fields and similar response properties synchronize robustly with zero time lag, whereas neurons that do not share the same receptive fields do not synchronize. Importantly, it is the response features of the neurons, rather than their spatial separation, that determine the vigor of synchrony. Neurons several millimeters apart in the same or different stages of the visual system and even across the two cerebral hemispheres have been shown to come together in time transiently by gamma-frequency synchronization. The interarea and interhemispheric

24. Gray and Singer (1989) and Gray et al. (1989) dubbed bouts of gamma oscillations as "visual sniffs," referring to the sniff-induced large-amplitude gamma oscillation in the olfactory bulb, described earlier by Walter Freeman, Gray's mentor (see Freeman, 1975). Although Singer consistently gives credit to von der Malsburg (1985) for the theoretical implication of synchrony in binding, Jung's cultural influence is hard to dismiss. This is reflected by Singer's consistent use of the term "synchronicity" (e.g., Fries et al., 1997; Singer, 1999; Engel et al., 2001). Eckhorn et al. (1988) also concluded that gamma oscillations may be a potential solution to the binding problem, using a similar experimental setup and reasoning. Synchrony and synchronicity refer to the same mechanism. I avoid using the term "synchronicity" because of its Jungean overtones.

25. For a historical survey of observations of gamma-frequency oscillations in humans, primates, and other animals, see Gray (1994).

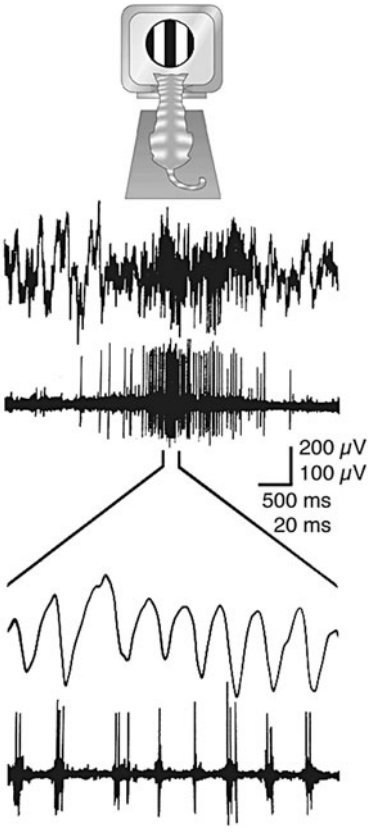

Figure 9.1. Stimulus-induced gamma oscillation: field potential and filtered multiple-unit responses recorded from the primary visual cortex of the cat. Movement of the visual stimulus in the preferred direction of the largest amplitude units evoked rhythmic firing and field oscillation at gamma frequency (40 hertz). Note the correlation of the field and unit firing (visible at the lower, faster traces). Reprinted, with permission, from Gray and Singer (1989).

synchronization of neuronal pairs or groups occurred primarily during the stimulus-induced transient oscillations.

Support for the internally organized nature of oscillation, as opposed to stimulus-driven synchrony, comes from experiments in which multiple neurons from two recording sites in the motion-sensitive middle temporal area of the waking monkey were activated by a single moving bar or two bars. When the neurons at the two sites were activated by two bars moving together over the receptive fields and in the preferred directions of the neurons, oscillatory coupling was rarely observed, even though neurons at both sites were activated. In contrast, when a single, longer contour activated both neuronal groups, they robustly synchronized. The "oneness" of the objects was therefore reflected by the

gamma-frequency coherence of unit activity and not by the similarly increased discharge rates.[26]

A more direct relationship between neuronal synchronization and behavior has been obtained in interocular rivalry tasks in cats with strabismic amblyopia.[27] Light responses induced similar changes in firing rates of V1 neurons from both eyes. However, synchronization among neurons was reduced when fine gratings of slowly moving stimuli were projected to the amblyopic eye. Previous behavioral experiments showed that these gratings were difficult to resolve by the amblyopic but not by the dominant eye. In a related experiment, rivalry between the two eyes was tested by using two mirrors through which different patterns were presented to the two eyes. Because perception in strabismic animals alternate between the eyes, this perceptual alternation can be used to examine how neuronal responses to stimuli change when they are perceived or excluded from perception. During binocular stimulation, each eye viewed grating stimuli of the same orientation but drifting in opposite directions. Neurons in visual areas V1 and V2 showed strong synchrony when the dominant eye was stimulated with the proper orientation, and synchrony was even enhanced after introduction of the rivaling stimulus to the contralateral eye. The reverse was the case for the losing eye.[28]

These animal experiments indicate that timing by synchrony is an alternative mechanism to the binding problem with numerous advantages over the connectionist model. Nevertheless, both approaches are based on the assumption that an object in the brain is built from its distinct physical elements. Each critical element is represented and identified by neuronal activity. The fundamental difference between the two models resides in the neuronal mechanism of the synthesis. In the hierarchical connectionist model, it occurs by the convergence of simple to ever more complex features. In the egalitarian binding-by-synchrony model, on the other hand, the simple representations are lumped together in one step by oscillations without the necessity of generating intermediate complexities. The neuronal knowledge generated this way is not the work of a handful of "smart" gnostic neurons, but rather reflects the aggregated wisdom of large numbers of individual cells. Nevertheless, in their basic configurations, both models assume a feedforward, bottom-up flow.[29]

26. Several exhaustive reviews summarize progress in the field of temporal binding (Singer, 1993, 1999; Gray, 1994, 1999; Singer and Gray, 1995; Engel and Singer, 2001; Usrey and Reid, 1999), so I refrain from citing the numerous original reports. See also reviews considering alternative views (Shadlen and Newsome, 1994, 1995, 1998; Shadlen and Movshon, 1999; Ghose and Maunsell, 1999; Reynolds and Desimone, 1999).

27. Strabismus or "squint-eye" condition is a developmental impairment, in most cases due to problems in eye muscle control. As a result, incongruent spatial information is projected from the two retinas to the brain. During development, one of the eyes becomes dominant, and information from the nondominant eye is "suppressed" (Attebo et al., 1998).

28. In the binocular rivalry experiments (Roelfsema et al., 1994; Fries et al., 1997), the eye mediating the detection of stimulus was verified by the direction of optokinetic nystagmus in the anesthetized cat. In a related human MEG study, gamma power was larger during rivalry from the eye that dominated perception than was gamma activity evoked by the nondominant eye (Tononi et al., 1998).

29. The binding-by-synchronization model is often discussed in the context of top-down operations. However, those features do not directly follow from the original theory.

Separation of figure and background is often mentioned as a major triumph of the oscillatory binding model. However, most of those experiments have been performed by using ambiguous figures. In most real situations, however, the figure and background are strongly related, and the context (background) determines the brain's interpretation of the figure. In these situations, it is the interrelationship of the two sets of stimuli rather than their segregation that has to be expressed by some neuronal mechanism. It is not clear how the feedforward or the binding-by-synchrony model can accomplish this requirement. Strictly speaking, only physiological synchronization can be established in anesthetized animals, but no perceptual binding. In the waking animal, on the other hand, the synchronization process may be under top-down control.

The issue of figure-background segmentation brings us back to the fundamental problem of the stimulus-brain response approach (Cycle 1). The tacit assumption in perceptual research is that the experimenter actually knows the attributes of the stimulus. The essence of this philosophy is that elements or features of an object activate different neuronal groups, and the applied program that should keep neuroscientists busy is to figure out how the binding of the elementary attributes is solved by the brain. The problem is that *the attributes of the object are not in the object.* Instead, the attributes of the object are generated by the observer's brain. As Gestalt psychologists have known for long, the whole is often faster recognized than its parts, indicating that object recognition is not simply representation of elementary features but the result of bottom-up and top-down interactions, in harmony with the architectural organization of the cerebral cortex. Before I address the importance and mechanisms of these top-down events (Cycle 12), let us consider some other important features of gamma oscillations.

Gamma Oscillations in the Human Cortex

The binding-by-gamma-oscillation hypothesis has a clear prediction for the human brain, as well. Although historically the binding problem was formulated for addressing the problems involved in visual object recognition, the idea that various attributes of a whole make up the whole is quite general and should apply to all modalities. Accordingly, every part of the cortex should be able to support gamma oscillations under the right condition. This generalization led to the hypothesis that consciousness, a state that requires linking global features of the brain–body–environment interface, can be linked to a defined electrophysiological process. Coherence measurement of MEG signals over the whole extent of the cerebral hemispheres indicates that significant coupling in the gamma frequency band is present in the waking brain as well as during REM sleep. However, sensory perturbation can easily reset the gamma rhythm in the waking state, whereas the same stimulus is largely ineffective during

REM sleep.[30] Irrespective of the interpretation, this is an important observation because all previous investigations of the human EEG assumed that the "desynchronized" scalp patterns of REM sleep and waking states are indistinguishable. However, further refinement of the localization and behavioral methods revealed that gamma is not ubiquitous but localized temporarily to areas engaged in a particular operation.[31]

As in animal experiments, enhancement of gamma-frequency power has been described in motor areas during, but more typically prior to, voluntary movement and in sensory-motor tasks. In another set of experiments, increased gamma activity over the frontal lobe was present intermittently during multistable mental rotation task in accordance with perceptual switching. Stereoscopic fusion of random-dot Julesz patterns[32] into a three-dimensional percept enhanced the power of gamma-frequency oscillation in the occipital cortex. Presentation of hidden figures, such as a Dalmatian dog in a patchy background or "moony faces" shown upright or inverted, elicited much larger gamma activity when the figure was perceived compared to no perception. Learned association between a visual and a tactile stimulus evoked a marked gamma oscillation after the presentation of the visual stimulus and elevated coherence between signals over the visual and sensory cortices. Significant difference in gamma power was reported between induced patterns by words versus pseudowords in both visual and auditory tasks. A common feature of all these experiments is that the induced gamma activity emerges at a variable latency between 150 and 300 milliseconds after stimulus onset, approximately at the time when stimuli acquire meaning.[33] Because the statistical features of the experimental and control stimuli were similar in many of these experiments, the waveforms of the early components of the evoked responses (i.e., < 150 milliseconds) were quite similar. Altogether, the late occurrence of context-dependent increase of gamma activity over multiple cortical areas is usually interpreted in favor of the

30. Ribary et al. (1991), Llinás and Ribary (1993), and Llinás et al. (2005). A technical issue is that the variability of the gamma cycle duration is much larger during REM than in the waking state. This variability could also explain why stimulus-induced resetting appears less robust. Note also that consciousness is assumed to be a qualitatively different state from unconscious state (Crick and Koch, 2003; Koch, 2004), whereas power of gamma frequency (and, in fact, all frequencies) and coherent coupling of oscillations differ only quantitatively in the sleep/wake cycle.

31. Detection of transient oscillation poses technical challenges (Pfurtscheller and Aranibar 1997). Because the emergent self-organized gamma oscillations are short-lived and not time-locked to stimulus features, time-domain averaging cannot detect them. One approach uses the time-varying spectra of the EEG tapered by a moving window of fixed duration (Makeig, 1993). Another alternative is to estimate the time–frequency power of the signal by means of a complex Morlet's wavelet transform (Percival and Warden 2000), applied to single trials, followed by averaging the powers across trials (e.g., Sinkkonen et al., 1995). The two methods are ultimately mathematically equivalent (see Cycle 4).

32. Julesz patterns are pairs of slightly-different random dot patterns, which, when viewed binocularly create the illusion of depth (Julesz, 1995).

33. This latency, of course, corresponds to the well-studied P300 component in time-averaged evoked responses (Näätänen 1975; Näätänen et al., 1987).

hypothesis that the self-organized gamma oscillation reflects a top-down cognitive process.[34]

The above observations also indicate that a coherent perception of an object involves synchronization of large cortical areas. This conclusion is in contrast to the experimental finding in animals, where mainly the cortical modules with the active units show increased and coupled gamma oscillations, whereas the main part of the surrounding cortex does not show such changes. However, the human observations may be simply due to the low spatial resolution of scalp recordings. If gamma oscillations in the human cortex play roles similar to those predicted by animal work, gamma oscillations should be confined to discrete active locations rather than being diffusely present over a wide cortical region. Intracranial and subdural recordings in patients, equipped with recording electrodes for diagnostic purposes, confirm this to be the case. Recording sites as close as 3–4 millimeters from each other in the visual cortex yielded quite different amplitudes of gamma oscillations. Importantly, sustained oscillations differentially occurred at different times of the task (figure 9.2), in a striking contrast to the short-lived oscillations over large areas observed in scalp recordings. The discrepancy between intracranial and scalp recordings indicates that the short bouts of oscillations detected by scalp electrodes actually correspond to localized events that are integrated over time and space.[35]

A particular striking correlation between working memory and gamma oscillation was observed by subdural grid recordings. Working memory is a hypothetical mechanism that enables us keep stimuli "in mind" after they are no longer available. The amount of information to be held at any given time is referred to as memory load, for example, the number of "nonsense" syllables to be stored when trying to repeat a toast salutation in a foreign language. The longer the string of the syllables, the larger the memory load. Experiments in epileptic patients, equipped with large numbers of subdural electrodes for diagnostic purposes, showed that gamma power increased linearly with memory load at multiple, distributed sites, especially above the prefrontal cortex. The power remained at the elevated level during the retention period but fell back quickly to baseline level after the working memory information was no longer needed. Overall, these observations support the more general idea that gamma oscillations are used in the brain for temporally segmenting representations of different items.[36]

34. Jagadeesh et al. (1992), Pfurtscheller et al. (1994), Salenius et al. (1996), Sanes and Donoghue (1993), Donoghue et al. (1998), Murthy and Fetz (1996), Başar-Eroglu et al. (1996), Pulvermuller et al. (1996), Tallon-Baudry et al. (1997, 2005), Miltner et al. (1999), and Rodriguez et al. (1999). There are many more experiments available in the literature than the handful listed above. Excellent reviews have summarized progress in this fast-growing field of cognitive neuroscience (Singer and Gray, 1995; Pantev 1995, König et al. (1996), Tallon-Baudry and Bertrand, 1999; Engel and Singer, 2001, Engel et al., 2001; Varela et al., 2001; Whittington and Traub 2003; Traub et al., 2004).

35. Tallon-Baudry et al. (2005) recorded with linear arrays of electrodes in the lateral occipital sulcus, the fusiform gyrus, and the posterior calcarine region. The subdural study of Sederberg et al. (2003) involved hundreds of subdural recording sites.

36. The idea that gamma oscillations could be used to hold sequentially encoded items in working memory comes from Lisman and Idiart (1995).

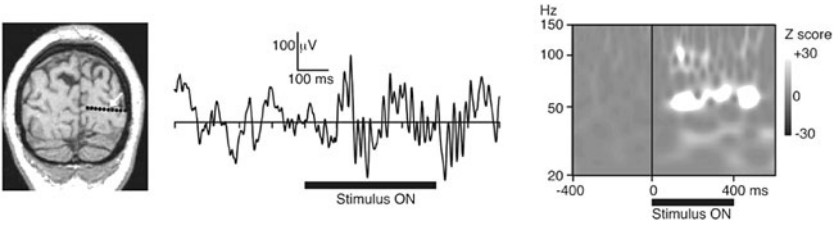

Figure 9.2. Gamma oscillations recorded from the human visual extrastriate cortex. Left: Depth multicontact electrodes were inserted perpendicularly to the sagittal plane in this patient with medically intractable epilepsy for presurgical seizure focus localization. Middle: Gamma-frequency oscillation evoked by a visually evoked stimulus that the subject attended. Right: Power distribution as a function of frequency and time. Light shade indicates a strong stimulus-induced power at 60 hertz, from 100 to 500 milliseconds after stimulus onset. Reprinted, with permission, from Tallon-Baudry et al. (2005).

Why Is Gamma Oscillation the Right Kind of Buzz?

The goal of synchrony for neuronal populations is the same as the goal of action potentials for single cells: forwarding messages to downstream neurons in the most effective manner. As discussed in Cycle 5, neuronal assemblies in the waking brain self-organize themselves into temporal packages of 15–30 milliseconds. They do so because presynaptic discharge within this time window appears to be most effective in discharging their downstream targets due to the temporal integration abilities of individual pyramidal cells.[37]

There is another, perhaps even more compelling reason for creating temporal windows repeatedly. So far, we have not considered the brain's perhaps most unique mechanism: the ability to change the connections among neurons adaptively. Neuronal connections are not created equal but are subject to use-dependent modification. There are at least two fundamental ways of how membership in neuronal coalitions can be altered. The first one is by forming physical connections between neurons or eliminating them. Although this method is the primary mechanism in the developing brain, it may continue in the adult brain, as well, albeit at a much reduced level. Another method is changing the synaptic strengths of

37. Synchrony of presynaptic terminals determines the total charge transfer. For discharging the postsynaptic neuron, time integration over 15–30 milliseconds appears optimal (Harris et al., 2003). For other needs, e.g., activation of postsynaptic NMDA channels, the temporal window of effective synchrony might be wider. Von Malsburg (1985) and Singer (Konig et al., 1996; Singer, 1999) postulated that "coincidence detection" in the 1- or 2-millisecond temporal window is needed for temporal coding, but to date, there is little evidence for the occurrence of such tight synchrony in the waking neocortex. Riehle et al. (1997) reported on behavior-dependent occurrence of spikes within 3 milliseconds in the monkey motor cortex, which they interpreted as evidence for coincidence detection. However, because the identity of the recorded neurons could not be revealed, the possibility could not be excluded that the pairs represented monosynaptic discharge of an interneuron by its presynaptic pyramidal neuron partner(s). In support of the latter explanation, the discharge probability between monosynaptically connected pyramidal–interneuron pairs is modulated by ongoing behavior (Csicsvari et al., 1998).

existing connections. There are two fundamental requirements for affecting synaptic strength: sufficiently strong depolarization of the postsynaptic neuron and appropriate timing between presynaptic activity and the discharge of the postsynaptic neuron.[38] Because both mechanisms are affected by the gamma-oscillation–mediated synchronization, adjustment of synaptic strength is a perpetual process in the cortex (figure 9.3). In recent years, it has been possible to measure the critical time window between the activity of the presynaptic (sending) and postsynaptic (receiving) neuron, which showed that every single time a postsynaptic neuron fires in a manner that the discharge leads to an increase of free Ca^{2+} in the dendrites, the previously or subsequently active presynaptic connections are modified.

The important information for us in the present context is that the critical temporal window of plasticity corresponds to the length of the gamma cycle. For my money, spike-timing–dependent plasticity, as the phenomenon is now widely known, is among the most important discoveries in cortical neurophysiology because it highlights the essential role of spike timing in modifying network connectivity, an undisputedly fundamental brain mechanism.[39] Thus, even if gamma oscillation proves to be irrelevant for the binding problem, the oscillation remains a central timing mechanism essential for synaptic plasticity. On the other hand, gamma oscillations may link the problem of binding to plasticity. This is because synchronization by gamma oscillations results in not only perceptual binding but, inevitably, modification of connections among the neurons involved. Synaptic modifications can stabilize assemblies representing currently experienced conjunctions. In turn, these use-dependent changes increase the probability that the same assemblies will be activated upon future presentations of the same stimulus even if the stimulus is somewhat modified in the meantime. The assembly bound together by gamma-oscillation–induced synchrony can reconstruct patterns on the basis of partial cues because of the temporally fortified connections among neuron assembly members.

38. Until recently, it was assumed that connections among neurons are created during early development and that those connections stay forever. However, recent *in vivo* imaging experiments tell a different story by demonstrating a slower paced, nevertheless continued, motility of dendritic spines in the adults, a method of wiring-based plasticity (Chklovskii et al., 2004). Synaptic plasticity was first demonstrated by Bliss and Lømo (1973), launching perhaps the most intense research in neuroscience (Bliss and Collingridge, 1993; Kandel and Squire, 2000; Johnston et al., 1996; Magee et al., 1998). Historical events leading to the discovery of LTP are discussed by Craver (2003). A third mechanism of brain plasticity is by replacing neurons and creating new ones. Neurogenesis is firmly established in the olfactory epithelium and in the dentate gyrus of the hippocampus (Gage, 2002).

39. The role of temporal order in synaptic plasticity was first discovered by Levy and Steward (1983) and was predicted by the rules of Pavlovian conditioning (Pavlov, 1927). See also Sejnowski (1977) and Stanton and Sejnowski (1989) for a theoretical treatment for the importance of spike timing. Spike-timing–dependent plasticity at the single-cell level is shown in Magee and Johnston (1997), Markram et al. (1997), and Bi and Poo (1998) and is reviewed in Kepecs et al. (2002) and Dan and Poo (2004). The relationship between gamma synchrony and plasticity has been modeled by Bibbig et al. (2001). This study hinges on the experimental demonstration that the time course of dendritic decay of Ca^{2+} approximately matches the gamma period.

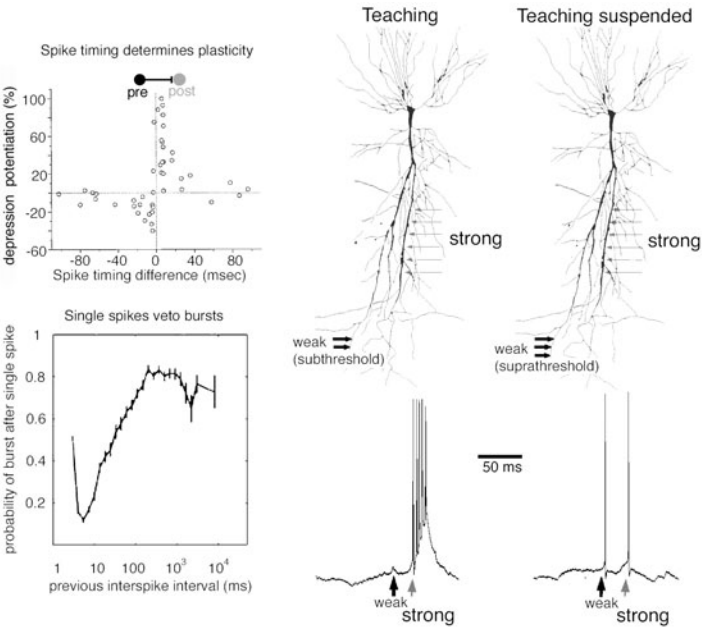

Figure 9.3. Gamma oscillation reflects the temporal window of synaptic plasticity. Left: If the onset of a presynaptic input (pre, which evokes only a subthreshold depolarization; weak) is followed by burst discharge in the postsynaptic neuron (post) within 40 milliseconds, the synapse gets stronger ("Hebbian teaching"; Reprinted, with permission, from Bi and Poo, 1998). Right: Once the weak input becomes strong enough to evoke a spike on its own (i.e., suprathreshold), teaching will be suspended. The reason is that a single spike can prevent the occurrence of burst discharge. The time course of the veto effect of a single spike (lower left panel) is similar to the time course of spike-timing–dependent plasticity (upper left panel). Reprinted, with permission, from Harris et al. (2001).

Gamma Oscillations Depend on Fast Inhibition

Gamma oscillations are intrinsic to the neocortex and can emerge in a small piece of tissue as localized activity. Importantly, the simultaneous, emerging "islands" sustaining gamma oscillations can occasionally get synchronized in widespread cortical areas.[40] As discussed in Cycle 3, inhibitory neuronal networks are essential in most oscillations. This is especially true for gamma-frequency rhythms, and a key player in the process is the $GABA_A$ receptor.[41]

40. In contrast to the highly localized transient gamma oscillation, induced by natural inputs, *in vivo* stimulation of the brainstem cholinergic nuclei induces widespread cortical gamma oscillation after 50–150 milliseconds even in anesthetized cats (Steriade and Amzica, 1996). For widespread gamma activity in humans, measured by MEG, see Ribary et al. (1991).

41. The idea that interneuron-mediated fast inhibition is critical in gamma oscillations came from the *in vivo* observations that several interneurons fire trains at gamma frequency, phase-locked to the

There are numerous ways to induce oscillations in the gamma band. The prototypic and simplest kind is when an isolated interneuron network is driven by a tonic depolarizing force (Cycle 3). Phasic excitation of interneurons by pyramidal cells can be readily prevented in slice preparations by blocking the ionotropic glutamate receptors by appropriate drugs or not including pyramidal cells at all in computer model networks. These approaches have attempted to address two main questions: how does the rhythm emerge and vanish, and what determines the oscillation frequency?

Oscillation in interneuron nets can be induced by a strong depolarizing input, such as a fast train of stimuli delivered locally *in vitro,* as first demonstrated by Miles Whittington, Roger Traub, and John Jefferys at University of Birmingham in England.[42] Direct recordings from interneurons and observing their patterns in computer models have shown that the frequency of network oscillation has little to do with the firing properties of individual neurons because none of them behaves like single-cell pacemakers. The average frequency of individual neurons can vary from 0 to 300 hertz, and the mean firing of the population does not correspond to the network frequency oscillations, either. Thus, frequency regulation should be sought in factors other than the firing frequency of the neurons. Both modeling and mathematics showed that the coherent oscillation of the whole network and the frequency of the rhythm are determined by the time course of the rise and decay of the inhibition, that is, the duration of time the population is prevented from firing. This critical variable was identified with the time constant of decay of the GABAergic current. The consequence of a silence or suppressed activity can be predicted from what we have already learned about oscillators: the introduction of a time constant, coordinated across a large part of a system, inevitably biases the system toward periodicity. Because the time constant of the decay of the inhibitory postsynaptic potentials, mediated by fast-acting $GABA_A$ receptors, varies from 10 to 25 milliseconds, the oscillation frequency can vary between 40 and 100 cycles per second. Pharmacological prolongation or shortening of the time decay of fast inhibition can decrease or increase the frequency of gamma oscillations.[43] The ubiquitous presence of $GABA_A$ receptors throughout

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field (Buzsáki et al., 1983; Bragin et al., 1995a). For recent reviews, consult Miller (2000), Buzsáki and Chrobak (1995), and Engel et al. (2001). *In vitro* rhythms are discussed in Traub et al. (1999, 2004). Nancy Kopell's review (Kopell, 2000) is an excellent introduction to the mathematical problems of gamma oscillations and oscillatory coupling.

42. Whittington et al. (1995).

43. Enhancing or blocking $GABA_A$ receptors slows or accelerates the rhythm, respectively, providing strong support for a critical role of this receptor in gamma-frequency regulation (Whittington et al., 1995; Traub et al., 1996, 1999; Wang and Buzsáki, 1996). Bartos et al. (2002) showed biexponential decay of the $GABA_A$-receptor–mediated inhibition between basket cells with a fast constant (2–3 milliseconds) followed by a longer decay. The critical aspect of the inhibition depends on the model. It can be the time constant of the decay or rise time of the postsynaptic potential, shunting effect of inhibition, or their combination in the various models (Kopell et al., 2000; Vida et al., 2006). In a noise-dominated interneuronal network, the oscillation frequency depends more on the shortest synaptic time constants (delay and rise time) than on the longer synaptic decay time (Brunel and Wang, 2003).

the brain explains why gamma-frequency oscillation can be found virtually everywhere. Another mechanism that facilitates synchrony among local interneurons is direct electrical communication in the form of gap junctions. These are low-resistant junctions that provide strong coupling between neighboring interneurons and facilitate the synchronous occurrence of spikes bidirectionally.[44]

Although gamma oscillation in interneuron networks helped our understanding the basic principles, isolated interneuron networks do not exist in the working brain. In the intact cortex, interneurons are embedded in large-scale excitatory networks, and both principal cells and interneurons are phase-biased by the oscillations, as shown by the intracellularly recorded excitatory and inhibitory postsynaptic potentials and the phase-locking of their action potentials. Although the decay time of the $GABA_A$ receptor remains the main cause in determining the oscillation frequency, other factors such as shunting inhibition, the magnitude and decay of the excitatory postsynaptic potentials and spike afterpotentials are additional time constants that can affect the oscillation. Nevertheless, the contribution of inhibitory postsynaptic potentials remains more critical for the extracellularly recorded power in the gamma frequency band than is the contribution of excitatory potentials. At the population level, this is amply reflected by the largest power of gamma currents near the somatic layers, where most inhibitory terminals are concentrated.[45] In the presence of principal cells and interneurons, a new competition emerges between inhibition-timed and principal-cell–timed occurrences of action potentials in inhibitory neurons. The synchronously discharging interneurons inhibit both each other and the pyramidal cells with a similar time course, allowing them to discharge most easily after the decay of inhibition. On the other hand, if a few pyramidal neurons happen to discharge in response to some input, the situation changes dramatically. The reason is the high efficacy of the excitatory synapse between principal cells and interneurons.[46] Discharge of a single pyramidal cell can initiate spikes in its target

44. Gap junctions are present mainly among the same types of interneurons (Katsumaru et al., 1988; Fukuda and Kosaka, 2003; Gibson et al., 1999; Tamás et al., 2000). Dendrites and somata of interneurons can be coupled by one or as many as 16 connexin-36 type gap junctions (Bennett and Zukin, 2004), with estimated coupling values of 0.5–1.5 nanosiemens (Galarreta and Hestrin, 2001). Gap junctions may help to reduce the heterogeneity problem inherent in interneuron networks (Traub et al., 2001). The role of gap junctions in gamma-frequency oscillation is illustrated by the reduced gamma power in connexin-36 gene knockout mice (Hormuzdi et al., 2001; Traub et al., 2003; Buhl et al., 2003; Connors and Long, 2004).

45. Both *in vivo* and *in vitro* findings show that the major part of the intracellular and extracellular gamma power is brought about by the fast-firing basket and chandelier neurons (Bragin et al., 1995a; Fisahn et al., 1998; Penttonen et al., 1998; Csicsvari et al., 2003; Mann et al., 2005).

46. Miles (1990) observed high reliability of excitatory postsynaptic potentials between pyramidal cells and unidentified interneurons. Gulyás et al. (1993b) showed that such highly reliable excitatory postsynaptic potentials are mediated by a single release site. Pyramidal cells often form clusters of multiple synapses on interneuron dendrites and can form contacts on cell bodies, as well (Buhl et al., 1997; Ahmed et al., 1997). Csicsvari et al. (1998) demonstrated high reliability of spike transmission between pyramidal cells and interneurons in the behaving rat. For neocortical pyramidal cell–interneuron connections, see Swadlow (2003).

interneurons, and the evoked interneuron spikes can dictate the time course of inhibition. The spiking pyramidal cells therefore introduce a novel phasic component, which can enhance or interfere with the oscillation. This unpredictable interaction is perhaps the main reason for the fragility and transient nature of gamma oscillations in the intact brain.[47] Although a very small fraction of principal cells are active at one time, their convergence on interneurons explains why the discharging pyramidal cells lead the interneuron action potentials by a few milliseconds.[48]

The phase-leading of principal cells in gamma oscillations raises an important issue.[49] Are subsets of spikes in principal cells dedicated for the initiation and maintenance of a rhythm? If so, the oscillation-related spikes may not be used for information transmission.[50] This does not appear to be an energetically efficient arrangement. The alternative solution is that spikes generated for the transmission of information and the initiation of the rhythm are the same, as has been suggested by the binding-by-gamma hypothesis in the visual cortex. Although pyramidal neurons in the visual cortex occasionally fire at gamma frequency in response to a relevant stimulus, firing patterns of single principal neurons are

47. Without external perturbations, gamma oscillation may be sustained, provided that the depolarizing and hyperpolarizing forces are balanced and coordinated. Such persistent gamma can be induced in small cortical slices *in vitro* by drugs that tonically depolarize both pyramidal cells and interneurons, e.g., carbachol, kainate, or metabotropic receptor agonists (Fisahn et al., 1998, 2002; Gillies et al., 2002; Mann et al., 2005). These *in vitro* studies also demonstrate that NMDA and $GABA_B$ receptors are not necessary for gamma oscillations.

48. The earliest model of gamma-frequency oscillations in the olfactory bulb assumed that the period of the oscillation is determined by the axon and synaptic delays in a reverberatory principal cell–interneuron local circuit (Ahn and Freeman, 1974; for a related model in the hippocampus, see Leung, 1992, 1998). The reverberation idea was based mainly on the observation that interneurons fired at an approximately one-quarter cycle phase delay after the pyramidal cells. The same reverberation model was used by Andersen and Eccles (1962) to explain the much slower theta rhythm. The presence of gamma in the purely interneuron network demonstrates that axon conduction delay is not the key variable for determining the oscillatory frequency.

49. Another potential source of synchronization in the gamma band is the postulated gap junctions between the axons of pyramidal neurons. Traub and colleagues have presented numerous arguments, computational models, and experimental data in favor of axonal gap junctions (Schmitz et al., 2001; Traub et al., 2002, 2003, 2004).

50. Gray and McCormick (1996) describe a special type of presumably excitatory cell in the visual cortex, which fires rhythmic bursts of spikes at gamma frequency upon tonic depolarization. They suggest that these "chattering cells" possess pacemaker properties and are critical for the emergence of network gamma oscillations. It is not clear, though, how a small group of excitatory cells can impose a rhythm on the principal cells, given the low reliability of single excitatory synapses in the neocortex. It is also not clear how excitatory postsynaptic potentials of chattering cells, exciting dendrites of the principal cells, can time the occurrence of action potentials, given the low-pass filtering effect of the dendrites. Interneuron-induced inhibitory potentials with fast kinetics and impinging on the somata of pyramidal cells are more efficient in regulating spike timing. Furthermore, Steriade (2004) has questioned whether chattering cells compose a special group, given that many pyramidal cells can burst at gamma frequency, provided the right depolarizing conditions. The resonant properties of pyramidal neurons, on the other hand, might further enhance the propensity of cortical circuits to oscillate at gamma frequency (Steriade et al., 1991; Llinás et al., 1991; Penttonen et al., 1998).

often characterized as irregular.[51] For the maintenance of a distributed gamma oscillatory network, it is not necessary that principal cells discharge at the network frequency. However, when a discharge occurs, its timing is constrained by the ongoing cycling inhibition. In turn, spikes of pyramidal cells will contribute to the timing of the action potentials in the surrounding interneurons.

Viewed from the latter perspective, the physiological cause for the occurrence of gamma-frequency oscillation is the elevated discharge of pyramidal cells coupled with the pacing of $GABA_A$-receptor–mediated local inhibition. Therefore, gamma activity is expected to arise in cortical areas with elevated firing of principal cells. Nevertheless, no single neuron in the oscillating network can be pointed to as the leader of the rhythm. Instead, principal cells and interneurons contribute equally to form a single oscillator. The implication is that small and large networks produce the same kind of rhythm and that the portions of the oscillator do the same as the whole. Can such distributed network oscillators with fractal features grow in size ad infinitum?

Coupling Distant Gamma Oscillators

The frequency of gamma oscillations is similar in mice, rats, cats, monkeys, and humans. The perpetuation of the rhythm across species also indicates that the size of the network is of secondary importance and that mechanisms exist to preserve timing across longer distances in larger brains. As discussed above, coherent gamma oscillations have been observed between structures set apart by large distances, including the primary visual cortices in the two hemispheres, in both humans and animals with smaller brains. Do such coherent oscillations occur because the participating neurons are part of a single oscillator growing in size, or should they be considered separate local oscillators that are coupled by some efficient mechanism? In both cases, the problem to be addressed has to do with the axon conduction delays.[52]

Let us first consider a single oscillator that grows in size. In the small-world-like structural organization of the neocortex, the synaptic path lengths remain the same independent of the size. Thus, as far as synaptic neuronal distances are concerned, there is no problem with size. The necessary shortcuts can be established by the long-range corticocortical connections, which have excitatory and (presumably) inhibitory components. In order to keep synchrony in phase, neurons at local and distant sites should discharge within the active cycle of the rhythm,

51. Firing patterns of cortical neurons can often be described by Poisson statistics (Bair et al., 1994; Shadlen and Newsome, 1994).

52. A third proposed scenario is that the thalamus acts as a pacemaker and is responsible for gamma coherence throughout the neocortex (Llinás et al., 2005). However, given the lack of interhemispheric wiring in the thalamus, it is unlikely that the thalamus can provide mean zero time-lag synchrony for cortical sites in the opposite hemispheres (Engel et al., 1991). In the absence of long-range cortical connections, even spindles remain segregated (Contreras et al., 1996; Khazipov et al., 2004).

which is limited to 5–10 milliseconds in the case of gamma oscillations. Some long-range axons with fast conduction speeds that meet these criteria do exist, but they are very few and limited mostly to interconnecting primary sensory areas (see Cycle 3).[53]

Another way of conceptualizing gamma synchrony between spatially distant sites is that two networks, such as the primary visual cortices in the two hemispheres, form two separate oscillators that are coupled by some links. Traub, now at Downstate Medical Center in Brooklyn, New York, and associates were the first to study the coupling of neuronal oscillators experimentally and in computational models.[54] They studied the synchronization of induced oscillations at two sites in the hippocampal slice preparation. In both the experiment and the associated model, the key requirement for synchrony was extra spiking of at least some interneurons in one network in response to excitatory inputs from the distant oscillating network. Because basket cells and other interneurons typically discharged a single spike per gamma cycle, and spike doublets occurred mostly when gamma became synchronized at both sites, the spike doublets in interneurons were taken as the necessary requirement for long-range synchrony. Modeling studies showed that the first spike of the interneuron was initiated by the local pyramidal cells, whereas after a short delay, another spike was triggered by inputs from the oscillating distant site. Provided that the later interneuron spike occurred in the same phase of the cycle as the first spike, the two sites maintained zero time lag synchrony.

It is important to recognize that once synchrony is established on a single gamma cycle, the two sites can remain synchronous for several cycles even without further synchronizing events. This is the major advantage of oscillatory synchrony and the main reason why synchrony can be established by relatively weak connections and few spikes. If the input from the distant sites arrives too late, due to long travel times, the extra interneurons spikes can prolong the inhibition and interfere with the ongoing oscillation, resulting in desynchronized activity. Further delays may lead to synchrony again, but this time the pyramidal cells are inhibited at every other cycle, firing effectively at half the frequency of the interneuronal gamma oscillation. Such gamma to beta oscillation shifts thus can emerge when conduction delays between the two sites are large.[55]

53. The advantage of long-range inhibitory connections, as opposed to excitatory ones, is that the effective time window of inhibition-mediated synchronizing effect is longer than that of excitation in relaxation oscillators. Excitation, to be effective, should arrive within the narrow duty phase of the cycle.

54. Traub et al. (1996) and Bibbig et al. (2002). Gloveli et al. (2005) suggest that gamma synchronization in the hippocampus is best in the CA3–CA1 axis, in contrast to theta synchronization, which is highest along the long axis of the hippocampus (Bullock et al., 1990).

55. A caveat is that the induced gamma-frequency patterns *in vitro* are supersynchronous, involving the discharge of virtually all pyramidal cells, as evidenced by the large-amplitude population spikes at gamma intervals (Traub et al., 1996). Therefore, the two-site synchrony studies under these conditions may be more relevant to epileptic synchronization than to physiological gamma coupling (Traub et al., 2005). Besides conduction delays, there are other explanations of the gamma to beta frequency shift, as pointed out by Kopell et al. (2000) and Bibbig et al. (2002).

Although the exact mechanisms of long-distance and large-scale gamma oscillations have yet to be clarified, the available findings clearly demonstrate that the major limitation of gamma coherence is the availability of fast-conducting fibers. Therefore, anatomical knowledge about the axonal diameter and myelinization of long-range connections, and the incidence of such fast-conducting fibers can predict the effective temporal coupling between cortical sites. Because primary sensory cortices but not frontal cortical areas are interconnected by large-diameter callosal fibers (see Cycle 2), high interhemispheric gamma synchrony is expected between sensory areas but not between frontal cortical areas.

As discussed in previous Cycles, long-range connections occupy an excessively large portion of brain volume, and therefore, large-diameter fibers are used sparingly. In large brains, such as those of elephants and cetaceans, the cortical networks are placed physically "too far" from each other, and even large-diameter fibers may prove too slow for synchronizing networks at distant cortical sites. Given the hypothesized importance of gamma-frequency synchronization in cognitive operations, we can conjecture that brains larger than that of *Homo sapiens* are less optimal for global performance because of suboptimal functional connectivity and, consequently, less effective temporal synchrony.[56]

Synchrony Can Be Brought About by External or Centrally Generated Oscillations

There is no a priori reason why information should be transmitted in a rhythmic fashion. In principle, a computer or any household electronic appliance could perform pretty much the same manner if information was moved according to a random temporal schedule, instead of a precise clock, as long as the steps at different levels were coordinated by some mechanism. In short, the key mechanism is synchrony for the sake of effectiveness; rhythm just happens to be a convenient physical and biological solution for synchrony.

Neurons can be brought together into short temporal windows by two general mechanisms. One is synchronization by a strong punctuate stimulus, and the other mechanism is emergent, self-generated synchrony.[57] Synchronously discharging neurons would exert the same effect on their targets, independent of the mechanisms

56. Although, to date, there is no experimental basis of such conjecture, ironically it is as good as any available hypothesis attempting to explain the superior performance of the human brain. Long conduction delays in whales can also be the reason for hemispheric independence and the observed unihemispheric sleep in these large-brain animals. For a counterpoint on brain size/complexity and intelligence, see Emery and Clayton (2004).

57. Internal or central synchronization is defined by a statistically significant covariation in firing probability of two neurons or a group that cannot be accounted for by their stimulus-locked covariations.

that brought about the synchrony. Most studies investigating the role of gamma-frequency oscillations in binding used stimuli that are either stationary or moving at a constant slow speed. The emerging oscillations are induced by the input in the sense that the onset of the rhythm and the oscillatory cycles do not have a precise temporal relation to the timing of the external event. However, the effect of temporally dynamic stimuli is quite different. For example, single neurons in the medial temporal area of the macaque monkey—several synapses downstream from the retinal input—can encode the moment-to-moment changes of a moving signal with a temporal precision of a few milliseconds between stimulus repetitions.[58] If changes of the external stimuli occur faster than the internally generated gamma frequency, intrinsic gamma will not emerge. This behavior is predicted by the nature of relaxation oscillators (Cycle 6). External stimuli can be conceived as perturbations that, when appropriately timed after the duty cycle, can advance the phase of the next cycle. If the input is irregular, the output of the forced "oscillator" (now without a rhythmic output) will also be irregular but time-locked to the input. We have described such pattern-following mechanism in rat pups, where the timing of cortical spindles reflected the trigger signals from muscular activity (Cycle 8).

If neurons are already engaged in internal synchronization, the external stimulus will compete with the central oscillator, and the outcome depends on the relative timing and strength of the external input and the propensity of the internal oscillator. The stimulus may be ignored, or it may enhance or quench the internal oscillation. In an experimental test of these ideas, Reinhard Eckhorn and colleagues from the Philipps University of Marburg, Germany, examined the perturbation of centrally generated gamma oscillations by stimulus-locked synchronized signals in V1 and V2 cortex of anesthetized cats. With increasing amplitude of fast transient movements, the internally induced power of the oscillation was gradually reduced, whereas the power of stimulus-locked events increased (figure 9.4). These experiments point to the paramount importance of the oscillation: synchrony. If synchrony is achieved by other means, such as strong inputs, oscillation is not needed. On the other hand, if the input is not sufficient to provide synchrony, the brain generates it by means of oscillations. Similar experiments were done also in the waking monkey. Rapid changes of the retinal image due to sudden movement of the object or transient changes in its contrast reduced the power of induced central oscillations. Position change of the object's image on the retina, due to fast vibration of the eyes at approximately 60 per second, called microsaccades, produced similar effects.[59]

A fast-moving stimulus, unless tracked by eye movements, does not allow for

58. Bair and Koch (1996), Bair et al. (1994), and Buracas et al. (1998).

59. Kruse and Eckhorn (1996); Eckhorn (2000). The frequent occurrence of saccadic eye movements in the waking animal may be another explanation why visually induced gamma oscillations are often larger in the anesthetized preparation where the eye position is fixed. For the precision of signal timing across the visual system, see Schmolensky et al. (1998). Ahissar and Arieli (2001) emphasize the active role of microsaccades in perception.

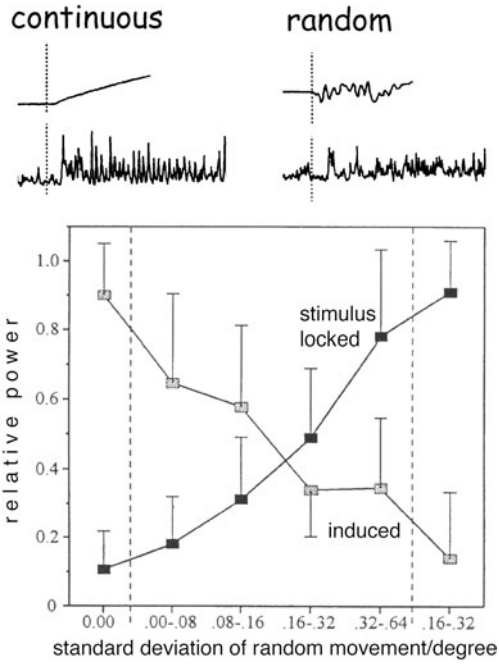

Figure 9.4. Internally induced and stimulus-triggered synchronous activities compete with each other. Top: Single-trial multiple-unit responses in the visual cortex, induced by a smoothly moving stimulus (left) or by sudden "jerky" changes of the visual scene (right). Note highly rhythmic activity at gamma frequency (30–60 hertz) in response to the continuously moving signal. In contrast, randomly moving stimuli evoked responses that were dominated by stimulus movement with no rhythmic component. Bottom: Adding increasing levels of random movement progressively decreased the stimulus-induced gamma-frequency power. Reprinted, with permission, from Kruse and Eckhorn (1996).

in-depth examination of stimulus features. The competition between detection of position and identification of the moving object also raises the important question of the necessary lifetime of cell assemblies in binding. One hypothesized advantage of the binding-by-gamma hypothesis is its multiplexing ability, which allows for the fast alternation of assemblies perhaps in successive gamma cycles. The important question is whether the same or different assemblies can be activated in successive gamma cycles. In principle, the alternation feature could be useful for the segregation of figure and background. However, neuronal activity in just one gamma cycle may not be sufficient for obtaining a consensus of distributed neurons and to induce the expected percept. This drawback is indicated by both our limited ability to perceive details of fast-moving objects and stimulation experiments of the human cortex. Brief electrical stimulation of the somatosensory cortex in waking patients can be detected but never described as "feelings." Only when trains, lasting from 200 to 500 milliseconds, are applied

do subjects report a sensation of touch.[60] The temporal window requirement places the induced gamma oscillations into a different perspective. It is possible that the function of the self-generated oscillations is to engage the same or systematically growing cell assemblies for sufficient duration necessary for subjective perception. In support of this idea, shortening the lifetime of the assemblies by stimulating the somatosensory cortex shortly after touching the skin can *prevent* sensation. A full assessment of the assembly lifetime window hypothesis will require large-scale recording of neuronal activity, a method that has the sufficient time and single-neuron resolution to examine the buildup and decay of neuronal assemblies and the impact of external perturbations on self-organized interactions.

The Content of Gamma Oscillations: Insights from Insects

Model systems are always a trade-off, giving up some direct relevance for simplicity. Consider olfactory perception in insects as a model for visual perception in higher mammals. Yet, these entirely different sensory systems have at least one thing in common: stimulus-induced gamma oscillations. The technical advantages of using insects over mammals are enormous. The principal enemies of the physiologist are movement-induced artifacts caused by breathing and vessel pulsations in mammals. The head of an insect with the brain can be fixed without the use of anesthetics that profoundly change the dynamics of the brain. For extra mechanical stability, the head can be separated from the body without major consequences. Biologically relevant stimuli can be delivered to the head sensors with high precision. Despite the small size of neurons, very complex physiology can be performed under convenient visual control in drug-free, sensing, and essentially intact preparations.

Gilles Laurent and colleagues at the California Institute of Technology have been working on the problem of coding of olfactory information. Their favorite animal is the locust because of its well-described anatomy of the olfactory system. Odorants exert their effects slowly, providing ample time for the experimenters to study the temporally evolving patterns. One such pattern is a transient oscillatory field response at gamma frequency that evolves over repeated presentations in the antennal lobe, mushroom bodies, and the beta lobe, three sequentially

60. Libet (2004). Similarly, transcranial magnetic stimulation of the occipital area induces phosphenes (tiny moving dots of light or stars) but no pattern sensation (Amassian et al., 1998). A general problem with direct brain stimulation methods is that the electrical pulses not only evoke supersynchronous discharge in neurons as a function of distance from the electrode but also inevitably recruit strong inhibition, which silences spiking activity for much longer time than the physiological suppression of activity brought about by gamma oscillations. The minimum time of perceptual switching when observing ambiguous figures may be related to the lifetime of induced gamma oscillations.

connected stages of olfactory processing in insects. Both projection neurons and GABAergic interneurons of the antennal lobe display membrane oscillations, coherent with the extracellular field potential, much like in the mammalian cortex. Spiking of the projection neurons shows unique firing patterns that evolve over 1–3 seconds, a really sluggish response. Different odorants activate different sets of cells, indicative of some spatial representation of odors. However, many neurons respond to several odorants, and the temporal patterns of spike responses are characteristic to different odorants and concentrations. Laurent observed that at a certain time after the odorant presentation, the individual spikes become phase-locked to the induced gamma cycles as well as to other simultaneously recorded neurons.

Are oscillations and the fine temporal patterning of spikes essential for odor recognition, or are they simply a byproduct of the circuit, a sort of correlated noise? By blocking $GABA_A$ receptors pharmacologically, synchronization of projection neurons in response to odorants is impaired, pointing to the importance of inhibitory receptors in the generation of gamma oscillations.[61] Importantly, whereas blocking the fast $GABA_A$ receptors in the antennal lobe abolished gamma waves and the oscillation-guided timing of the projection neurons, it spared the spike patterning of individual neurons on the longer temporal scale. In an elegant series of experiments, Laurent's group asked whether such "desynchronization" in the antennal lobe has any consequences to the behavioral response of the animal and how such fine temporal structures could be exploited for extracting information about the odors by downstream networks.

For the behavioral experiments, they switched to honeybees and showed that the basic physiological patterns are similar to those observed in the locust. They trained the bees to discriminate between odorants of different chemical composition ("easy task") or between molecularly similar odorants ("difficult task"). The blockade of gamma oscillations in the antennal lobe impaired the bees in the difficult task, but they could still distinguish the dissimilar odorants. The experimenters reasoned that gamma oscillation of neuronal assemblies in the antennal lobe is functionally relevant and that the fine temporal structure of neuronal spiking is essential for the segmentation of stimulus representation. To test this hypothesis, they went one important step further and recorded from neurons in the beta lobe, two synapses downstream from the antennal lobe. Similar to the projection cells of the antennal lobe, beta-lobe neurons display odor-specific firing patterns. Because the "observer" neurons are upstream from the antennal lobe cells, they examined whether the fine temporal relationship among the input neurons is relevant to the response patterns of the observers. After screening for odorant-specific patterns in the beta-lobe neurons, $GABA_A$ receptors were blocked pharmacologically in the antennal lobe, resulting in the loss of gamma

61. Because GABAergic neurons in the locust antennal lobe do not emit action potentials, these observations add further support of the $GABA_A$ receptor time constant as the major source of gamma-frequency regulation. Gamma frequency in insects is lower (20–30 cycles per second) than in mammals (Laurent, 2002).

oscillation but not of the general response patterns of its neurons. Two observations were made. First, the discrimination of odors by the evolving firing patterns of the beta-lobe neurons was impaired. Whereas simple inspection of spike distributions during and following odor presentation could inform the experimenter whether cherry or citral odorant was delivered, following the loss of gamma oscillation in the antennal lobe, the neuronal responses in the downstream beta lobe became less distinct. The second observation was the emergence of new responses to odorants to which the beta-lobe neurons never responded with the oscillation intact.[62]

No matter how convincing these experiments in insects are, they do not, by analogy, prove that identical mechanisms are in action in the visual system of mammals. After all, there is no guarantee that the mechanism of stimulus coding in an insect has a lot in common with vision and other operations in a mammal. Similar proof should be provided in the more complex brains. Nevertheless, the experiments in insects do suggest that the fine temporal organization by oscillatory synchrony is a fundamental mechanism that may be valuable in many structures. If a constructive mechanism is invented by nature in simple organisms, more complex animals tend to exploit it. The findings also show that the information can be contained not only in the firing rate changes of individual neurons but also in the temporal relation of spikes in neuron pairs and assemblies. At this point, it is worth reiterating that gamma oscillations, and neuronal oscillations in general, are not "independent" events that impose timing on neuronal spikes but rather are a reflection of self-organized interactions of those same neurons that detect, transfer, and store information. Full exploration of this claim requires recording from large numbers of identified neurons and appropriate analysis methods.

Briefly . . .

The most characteristic field pattern of the waking, activated neocortex is gamma oscillation. Because of its low amplitude, the oscillatory nature of this EEG pattern was difficult to reveal by the early mechanical pen recorders, for which reason the waking scalp EEG pattern was generally referred to as "desynchronized." Gamma oscillations are ubiquitous throughout the brain. The main

62. A long list of reports describe the experiments summarized here (MacLeod and Laurent, 1996; Wehr and Laurent, 1996; Stopfer et al., 1997; McLeod et al., 1998; Stopfer and Laurent, 1999). For reviews, see Laurent (1999, 2002). A potential caveat is that insects can make a decision about the identity of odorants within 300–500 milliseconds, whereas the differences in firing patterns evolve over several seconds. Another criticism is that newborn rats are able to make olfactory discrimination yet only sniffing-related theta oscillations without the fast gamma are present at this young age (Fletcher et al., 2005). However, Laurent's group has also pointed out that discrimination between chemically distinct odorants in honeybees are still possible after pharmacological blockade of gamma oscillations, but the bees are severely impaired when chemically similar odorants are to be distinguished.

reason for this is that its generation depends primarily on the time decay of $GABA_A$-receptor–mediated inhibition and/or shunting. These receptors are uniformly distributed in the cerebral cortex and other brain regions. Because inhibitory postsynaptic potentials mediated by these neurons are quite reliable, they provide a more efficient means for timing than the notoriously unreliable excitatory postsynaptic potentials. Furthermore, the membrane of basket and chandelier neurons, the major suppliers of fast inhibition to the perisomatic region of principal cells, possess resonant properties selectively in the gamma frequency band, and these interneurons often fire in this frequency range. In addition to mutual inhibitory innervation, interneurons are also coupled by gap junctions. Due to the localized axon arbors of basket and chandelier cells and the local gap junctions, gamma oscillations in the cortex are often confined to a small piece of tissue. Coupling of distant gamma oscillators require fast-conducting conduits, which requirement may be fulfilled by the widespread axon collaterals of long-range interneurons and possibly by the long axons of some pyramidal cells. Phase coupling of induced gamma oscillations allows for the temporally synchronous discharge of activated groups in disparate parts of the cortex. The physiological importance of the gamma rhythm is supported by the observation that neuronal assemblies in the waking brain self-organize themselves into temporal packages of 15–30 milliseconds. This time window is most advantageous for neurons downstream from the assemblies because pyramidal cells integrate excitatory inputs most efficiently in this time range. Perhaps an even more compelling argument for the functional importance of gamma oscillations is that strengthening and weakening of synaptic links are best established within the time period of gamma waves by the mechanism of spike-timing–dependent plasticity.

Gamma oscillations have been hypothesized to offer a solution to the century-old "binding problem" of perception. Because different features of an object, such as color, texture, distance, spatial position, and smell, are processed in separate parts of the cortex by different sets of neurons, one should explain how they are bound into a complex representation in a matter of 200 milliseconds or so to "reconstruct" the physical object. An earlier solution of the binding problem is a hierarchical feature extraction in feedforward networks, the product of which is a set of "gnostic" neurons at the top. At each processing stage, features represented by the preceding stages are combined to gain ever more complex features. The gnostic neurons at the end of the hierarchy are believed to explicitly represent unique objects and concepts.

Although hierarchical organization and feature extraction in the brain cannot be denied, there are several problems with representations by gnostic units only. An alternative to the sequential feature extraction scheme is the temporal binding mechanism by gamma-oscillation–assisted temporal synchrony, a novel hypothesis of object perception that unleashed a new dialogue about the role of timing in the brain. In the "binding by synchrony" model, convergence of connectivity is no longer the main variable of feature extraction; rather, it is the temporal synchrony of neurons, representing the various attributes of objects, that

matters. The different stimulus features, embedded in the activity of distributed cell assemblies, can be brought together transiently by the temporal coherence of the activated neurons, which oscillate at gamma frequency. An attractive feature of the temporal binding hypothesis is that it offers a versatile coding capacity for feature combinations. In addition, cross-modality representations can be mapped directly onto each other, using essentially the same coding format.

Can a mechanism as simple as an oscillation solve such a complicated problem as binding? Perhaps not, but it may be an essential ingredient of the solution. It must be emphasized that temporal synchrony by oscillation and hierarchical feature extraction are not mutually exclusive mechanisms. Importantly, synchronization by gamma-frequency oscillation can be detached from the problem of binding. Even if gamma oscillation does not solve the issue of binding, oscillations in the gamma-frequency range remain a compelling timing/selection mechanism for neuronal communication.

Cycle 10

Perceptions and Actions Are Brain-State Dependent

> Complex systems do not forget their initial conditions: they carry their history on their backs.
>
> —Ilya Prigogine

The loss of our ability to communicate with the environment and control our skeletal muscles at will—in short, the loss of awareness—at the onset of sleep justifies the use of two discrete words for the separation of two distinct brain states: sleep and wakefulness. Being aware and not being aware of our surroundings are considered to be qualitatively different states. However, at any given moment, not all systems or subsystems are necessarily equally asleep or awake. Like in the damped oscillatory stages of sleep, our various physiological and subjective operations, emotions, and level of alertness also change systematically and periodically while awake. The optimal time of day for maximum athletic achievement or best cognitive performance varies and depends on the nature of the task. Even some trivial motor outputs, such as hand grip strength, and simple cognitive performance, such as multiplication, vary considerably. The variation of our motor and cognitive abilities is evident over periods of minutes, seconds, and even finer time scales.

Psychophysical measurements have already provided ample evidence that brain states characterized by various terms, such as arousal, vigilance, attention, selective or focused attention, expectation, anticipation, mental set, mental search, evaluation, surprise, emotions, motivation, drive, novelty, and familiarity, exert a strong influence on the brain's interpretation of sensory inputs prediction. Other hypothetical constructs, such as planning, preparation, decision, and volition,

also affect motor execution and the reaction time between sensory inputs and motor outputs. It is not clear, though, how these terms and especially their alleged neurophysiological mechanisms differ or represent the same or overlapping mechanisms. For example, the term "selective" or "focused attention" presupposes that some higher brain centers already "know" which aspects of the inputs are worth attending. Without some prior knowledge, the details of an object are available only after an object is identified. Gestalt psychologists have already demonstrated that the whole can amplify or suppress its constituents, implying some top-down brain mechanisms that bias sensation and perception. Clearly, there is more to perception than just feedforward hierarchical processing and temporal binding.

A "state" usually refers to a static condition, such as the solid, liquid, and gas states of water, with fast phase transitions between them. Cognitive states, however, are notoriously difficult to define. A brain state can be regarded as a transient equilibrium condition, which contains all aspects of past history that are useful for future use. This definition is related but not identical to the equally difficult concept of "context," which refers to a set of facts or circumstances that surround an event, situation, or object. Similar to "state," the term "context" implies some historical precedence; therefore, it invokes some feeling of dynamics. But how can such idealized variables, such as state and context, be created in the brain and defined objectively without the need of an "executive network" or homunculus and inevitable infinite regress? A promising approach is to explore the sources of response variability. Such an approach attempts to understand the neurophysiological mechanisms that give rise to the perpetual changes of brain dynamics, instead of dismissing the sources of variability as "noise" that emanates from the brain's imperfection.

Cycle 5 discussed the $1/f$ statistic of global brain activity as an idealized critical state, a perpetual phase transition that endows the brain with the ability to respond to external perturbations most effectively. However, the $1/f$ statistic is a historical product. It is a result of both intracortical connectivity and the integration of the various oscillations that evolve over time. At any given instant, different oscillators dominate the brain's landscape, determined by the memory of its long-term dynamics. This Cycle discusses how to evaluate the effectiveness of environmental perturbations against this time-evolving background. Because this background is not a constant equilibrium state, responses of brain networks are not expected to be constant, either. Evoked activity may reveal more about the state of the brain than about the physical attributes of the stimulus.

Averaging Brain Activity

Tracking the mean field changes of neuronal activity is, in principle, a reliable method for monitoring the spread of activity between anatomically connected

structures. This strategy is based on the well-established method of stimulus-evoked time averaging of brain potentials or metabolic changes in brain imaging experiments. The averaging approach has been the foundation of an active and successful experimental program in cognitive and experimental psychology.[1] The tacit assumption behind the averaging procedure is that an external stimulus produces something from nothing, where "nothing" is equated to a baseline of no neuronal activity or stochastic firing of neurons. Averaging is essentially a subtraction method, in which the invariant and variant response components are separated. The variability of the responses across trials is generally relegated as unexplained variance or "noise" that needs to be averaged out to reveal the brain's true representation of an invariant input. Because the physical features of the stimulus remain unchanged, the tacit assumption is that the brain's response should also remain constant. The trial-to-trial variability is attributed to uncorrelated noise in the background neuronal activity. In functional magnetic resonance imaging (fMRI), the responses are often pooled and averaged across subjects to further reduce the variance, irrespective of the subjects' personal histories.

A disturbing aspect of the additive "noise plus signal" concept has been the observation that the magnitude of spontaneous activity is often as big as the stimulus-evoked response, and the spectral components of the background and evoked activity are often quite similar. Viewing it from the time domain, the averaged waveform not only varies as a function of the background or spontaneous activity but also often incorporates features of the background. For example, no matter how many times a stimulus is presented in two different states, the average responses, collected for example during sleep and alert wakefulness, will remain characteristically different. This should not be so if the background was simply random noise. However, previous Cycles have already presented ample evidence that spontaneous activity that characterizes "brain state" is neither stationary nor random.

Changes of brain state are hard to predict from overt behavior on a moment–to-moment basis. On the other hand, momentary changes of the ongoing EEG can be precisely monitored and related to each other in time. Such quantitative comparisons point to an alternative source of evoked responses: phase resetting of ongoing oscillations.[2] The two competing models of evoked responses have different predictions that can be tested experimentally.[3] If the evoked response is the sum of independent noise and an added signal, then the power of the signal should increase after the stimulus in the frequency bands corresponding to the components of the average response. On the other hand, if the stimulus simply

1. See Hillyard and Kutas (1983) for evoked response exploration of cognitive processes. E. Roy John's book *Neurometrics* (John, 1977; see also John et al., 1998) is perhaps the most comprehensive source of clinical applications of scalp-evoked responses.

2. Stimulus-locked reordering of phase is common in biological oscillators. See, e.g., Winfree (1987) and Glass and Mackey (1988).

3. For a good introduction to evoked potentials, see Lopes da Silva (1993) and Vaughan and Arezzo (1988).

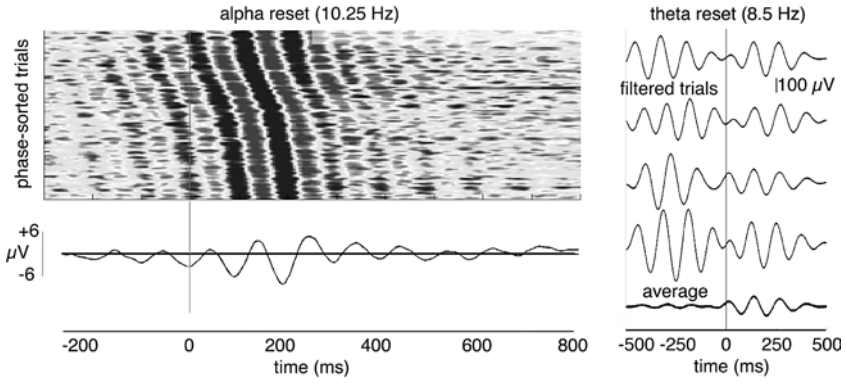

Figure 10.1. Phase resetting of ongoing oscillations. Left: Single-trial "evoked responses" from a posterior central scalp recording site, sorted according to the phase of ongoing alpha oscillation (top). Each horizontal line represents a single trial. The sigmoidal shape of the phase-sorted poststimulus alpha waves indicates the dependence on the phase of the prestimulus alpha oscillation. The bottom trace is an average "evoked response," that is, the mean of the phase-reset events. Modified, with permission, from Makeig et al. (2002). Right: Stimulus-induced phase reset of theta oscillations from filtered, single trials of subdurally recorded field potentials over the neocortex of a patient. Vertical line indicates the onset of visual probe items. The bottom trace is an average of several hundred trials. Note that neither the frequency nor the amplitude of the oscillation was affected by the stimulus. Modified, with permission, from Rizzuto et al. (2003).

resets an ongoing oscillator, no power increase is expected. Furthermore, the average stimulus-evoked response should contain damping oscillatory components whose frequency is identical to the background oscillation.

A particular striking example of oscillatory phase reset has been shown by Scott Makeig, Terry Sejnowski, and colleagues at the University of California–San Diego. They asked their subjects to press a button each time a target stimulus was presented on the video monitor in a small green square and to ignore the same stimulus presented at other, nontarget locations. They analyzed the responses to the ignored stimuli (figure 10.1). The first striking observation was that in the absence of alpha power prior to the stimulus, virtually no responses were elicited. On the other hand, when the background alpha power was high, the evoked response amplitude was also high, and the average "evoked response" was essentially a ringing oscillation, whose frequency was identical to the background alpha oscillation. When the individual responses were sorted as a function of the phase of the ongoing oscillation, the evoked response peaks did not have a fixed latency with varying amplitude, as would be expected by the noise-plus-stimulus model. Instead, the latencies varied systematically as a function of the phase of the ongoing alpha oscillation without much amplitude variance. In agreement with previous observations, fine-grain analysis of individual responses clearly showed that the ignored stimuli simply reset the phase of the

ongoing alpha oscillations.[4] Several spontaneous oscillators contributed to the evoked responses, including the visual cortex alpha, mu rhythm, and even frontal midline theta rhythms, illustrating the complex nature of scalp-recorded potentials.

The functional importance of the background cortical activity comes from another study, which examined the effect of just perceivable somatosensory stimuli. The electrical stimulation of the left or right index finger was adjusted so that only approximately 50 percent of the events were perceived and reported by the subject. The physically identical stimuli were detected only when they were preceded and followed by a sufficient power of alpha and theta activity not only in the somatosensory but also in the parietal and frontal cortical areas and when their presentation coincided with a certain phase of the ongoing oscillation. The stimulus-induced phase-locking or its absence, reflecting perceived and unperceived stimuli, respectively, diverged as early as 30 milliseconds after the electrical stimulation of the skin, suggesting that the perceptual "fate" of the input was destined by the state of the large-scale cortical network.[5] Near-threshold perception thus requires a special constellation of cortical oscillatory network activity, and the ongoing spontaneous activity is critical for the enhanced detection of the signal.

An important practical implication of the phase-reset model is that the components of the average evoked response are not representative of single responses. The individual responses are not simply a noisier version of the average response with fixed latencies. In fact, the component amplitudes of the average response reflect a combination of the amplitude and latency variability of the single responses. Therefore, no matter how tempting it is to speculate about the contribution of excitatory and inhibitory sources of the negative and positive components of the average, as is evident in numerous publications, no such top-down or reverse-engineering inferences can be made. The theoretical implication is that stimulus-correlated events reflect more the perturbation of spontaneous oscillations than de novo events. The external stimulus cannot be considered as the sole initial condition for the ensuing brain activity.

The behavioral relevance of phase resetting is further supported by the consistent observation that movement initiation and reaction times vary systematically as a function of phase of the scalp-recorded alpha rhythm.[6] Similar observations were made in relation to the robust hippocampal theta oscillations

4. Makeig et al. (2002, 2004). Such striking "alpha" ringing was first reported in the occipital cortex of rats (Klingberg and Pickenhain, 1967). Studying auditory responses, Sayers et al. (1974) raised the possibility that the average evoked response components reflected phase reorganization of spontaneous oscillations. Başar (1980) has repeatedly stressed the importance of oscillatory phase reset in evoked or induced responses.

5. JM Palva et al. (2005b) observed weaker but significant phase reset of faster frequencies, as well, indicating that the faster oscillations nest on the slower events.

6. In perhaps the earliest experiment on the topic, Bates (1951) used superimposition of scalp EEG of subjects instructed to make a succession of abrupt grips at a rate of about 10 a minute. In some subjects, the instant of motor performance tended to be related to a particular phase of the EEG alpha

in rats. Behaviorally relevant conditioning stimuli, predicting a reward, can effectively reset hippocampal theta oscillations and produce an average evoked response resembling a ringing oscillator. Conversely, when short electrical trains were delivered at the peak of stimulus-reset theta, long-term potentiation of the affected intrahippocampal pathways was elicited. The same electrical pulses delivered at the time of the trough did not produce potentiation. Because similar phase dependence of potentiation is also present during spontaneous theta waves in the intact animal, as well, these findings add further support to the similar nature of the spontaneous and evoked or phase-reset responses.[7] The observations in rodents are supported by neuromagnetic (MEG) studies in normal human subjects and by subdural EEG recordings in epileptic patients in a working memory task. MEG responses were recorded during presentation of a set of digits and a subsequent probe of the retained items. The stimuli reset the theta oscillation, and the duration of stimulus-related theta increased with memory load, with a limiting value of approximately 600 milliseconds for five to seven retained items.[8] Phase resetting of oscillators, in general, is expected by the intrinsic properties of oscillations, as discussed in Cycle 6. The firing patterns of neurons in both cortex and hippocampus are grouped to the trough of the local alpha and theta waves (Cycles 8 and 11); thus, they behave like relaxation oscillators despite the harmonic appearance of the macroscopic field potentials. The relaxation oscillation nature of the ongoing alpha and theta rhythms can explain their easy phase resetability.

The relaxation features of cortical oscillators also provide an explanation for the behavioral advantage of phase reset. Resetting an oscillator can create an optimal temporal relationship between cell assembly discharges and the information carried by the stimulus-related activity. If the input randomly arrives on opposite phases of the cycle without the ability to affect timing of the neuronal assemblies, the stimulus-induced effect may be enhanced or ignored. On

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rhythm. In a related experiment, Lansing et al. (1959) found that the shortest and longest visuomotor reaction times in some human subjects tended to fall at points in opposite phases of the alpha cycle. Recently, the phase of alpha oscillation on the P300 component of evoked potentials (a positive deflection that occurs approximately 300 milliseconds after the stimulus) in an auditory oddball was studied. The alpha phase at stimulus onset in single trials with a large P300 was significantly different from that in single trials with a small or no P300 (Haig and Gordon, 1998). The exact timing of motor execution, e.g., bar pressing in rats, varies as a function of the hippocampal theta cycle (Buño and Velluti, 1977; Semba and Komisaruk, 1978).

7. Huerta and Lisman (1993, 1995) did the in vitro experiments, which were confirmed in vivo by Holscher et al. (1997).

8. Buzsáki et al. (1979) described theta reset by click stimuli. These observations were recently replicated and extended (McCartney et al., 2004). However, in our recent (unpublished) experiments, a tonal go signal failed to reset theta activity while the rat was running in a wheel. Click stimuli may activate the vestibular system, as well, which may be critical for theta reset. See also Sinnamon (2005) for lack of phase reset of hippocampal theta. Phase reset of theta oscillations in humans was analyzed by Tesche, and Karhu (2000) and that of faster frequencies (7–16 per second) in a working memory task, by Rizzuto et al. (2003).

the other hand, if the input can bias the firing patterns of the neurons involved in the oscillations, the probability of ignorance can be decreased. Phase resetting, therefore, can selectively amplify the impact of afferent signals. This same reasoning may explain why under most circumstances the average evoked response reflects a combination of phase resetting of ongoing oscillations and enhanced power of activity. A very strong or salient stimulus can affect many more neurons than do the self-generated spontaneous oscillators. For example, highly arousing and salient stimuli not only can exploit ongoing brain dynamics but also can alter the brain state, as well, so that the newly created dynamics are very different from the prestimulus condition. Event-related "desynchronization," that is, a prompt shift from alpha and mu synchrony to dominantly gamma activity, is the typical example of such state change in brain network activity (Cycle 7). A medium-intensity stimulus may only slightly modify the ongoing oscillators such that the response is a combination of both enhanced neuronal activity and phase modification of the background oscillator(s). Finally, a weak stimulus may be able to reset the oscillator without otherwise modifying it. In the last case, the ongoing oscillator may enhance the impact of the weak input through stochastic resonance (Cycle 8) and can extract information of weak but well-timed signals coinciding with the duty cycle of oscillator.

The above discussion on the average evoked field responses also holds for induced rhythms, for example, the binding-associated gamma oscillation. Because most overt and covert behaviors are transient, their brain oscillation correlates are also short-lived. Although averaging short-time power spectra appears to be the perfect way to analyze brain–behavior relations (Cycle 9), the trial-to-trial variability of induced gamma oscillations should also depend on the time-evolved background context, an important issue addressed in Cycle 12.

Neurons Fire Best in Their Preferred Cortical State

The implication of the hypothesis of the concerted interaction between background and stimulus-induced activity is that there are specific network states in which neurons discharge optimally. In a series of high-profile reports, Amos Arieli, Amiram Grinvald, and Misha Tsodyks at the Weizmann Institute in Rehovot, Israel have systematically explored the relationship between spontaneous and evoked activity in the visual cortex of anesthetized cats.[9] First, they found that the probability of spike occurrence in single neurons was strongly related to the activity of the recorded field both in the vicinity of the unit and also several millimeters apart. This relationship of course is not surprising since it is the activity of the individual neurons that generates the extracellular field. Spiking

9. Arieli et al. (1996), Tsodyks et al. (1999), and Kenet et al. (2003). For the relationship between single neurons and population field activity in the neocortex, see Steriade (2001a,b); in the hippocampus, see Buzsáki et al. (1983).

in a single neuron is under the control of an assembly, and assemblies are under the influence of local control, and local networks are embedded in larger networks. However, their observations went beyond this general knowledge, made possible by a new tool for imaging membrane potential changes in large neuronal aggregates with a high spatial resolution. The method is optical imaging of local field potentials by applying a voltage-sensor dye that can measure the membrane potential changes of neurons and glial cells on the surface of the cortex. It is essentially the same method as electrode measurements of the field, except that the spatial resolution of the optical measurement is substantially better.

Using the surface imaging method, they have already demonstrated that different stimulus features, for example, the orientation, direction of motion, and spatial frequency of the visual stimuli, evoke unique spatial distributions of cortical surface activity. These patterns occur because in the visual cortex, neurons with similar response properties are clustered together, and visual features change gradually in the tangential direction along the cortical surface. Such a systematic representation of visual features is called a "functional map." Among the various features, orientation preference is the most prominent in the primary visual cortex.[10] Because each functional map results from the aggregate activity of a large neuronal assembly, one can probe the relationship between the map and an arbitrarily chosen neuron by identifying the constellation of stimuli that best drive the neuron. For example, if a vertical grating is most favored stimulus of the neuron, stimulation can be repeated numerous times, consistently discharging the cell and, at the same time, providing an average functional map. The evoked map is a graphic reflection of the aggregate activity of the nonrecorded peers with similar input preference and is called the neuron's "preferred cortical state." The interesting part of the experiment, however, was when the experimenters examined the relationship between spontaneous spike activity of the single cell and the spatial distribution of the field in the absence of visual input. Now, the trigger for averaging the field was the spontaneous occurrence of action potentials of the neuron. Remarkably, they found that the map generated this way was quite similar to the evoked functional map (figure 10.2).

The similarity of the single-spike–associated and visually evoked map can be explained by assuming that in the absence of visual stimuli spiking in the single cell occurred when the trajectory of activity in the network was most similar to the stimulus-driven case. In other words, the activity of visual cortical neurons in the absence of visual input is not noise but controlled predictably by the dynamically changing cortical states. In the absence of external inputs, a local cortical network wanders through various attractor states, each corresponding to the cooperative activity of a unique cell assembly. Examining long epochs of spontaneous cortical activity revealed that such patterns are far from random. On the contrary, most

10. The term "functional map" was coined by Hubel and Wiesel (1963). The tangential layout of the orientation columns exhibits a unique feature: iso-orientation domains are arranged in a pinwheel-like fashion around singularities, known as "pinwheel centers" (Braitenberg and Braitenberg, 1979; Swindale, 1982; Bonhoeffer and Grinvald, 1991). Around a pinwheel center, the preferred orientations change continuously by ± 180°, corresponding to clockwise and counterclockwise pinwheel centers. For a reader-friendly review on visual cortical maps, see Grinvald and Hildesheim (2004).

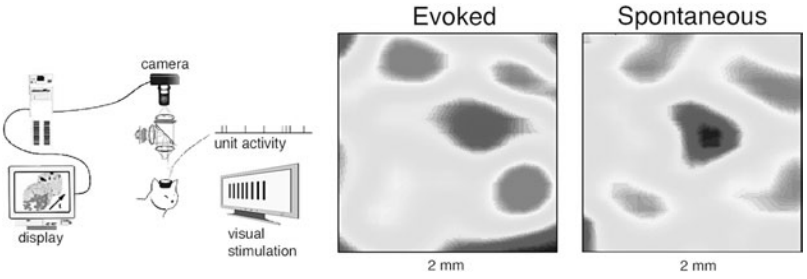

Figure 10.2. Firing patterns of single neurons are constrained by the cortical networks in which they are embedded. Simultaneous recording of the optical signal on the cortical surface and single-cell recording can be used to compare the relationship between the activity of single neurons and their network correlates (left). Movement of the visual stimulus in the preferred direction of a single unit evoked a characteristic spatial pattern on the cortical surface (middle). In the absence of visual stimulation, spontaneous activity time averaged by the occurrence of spikes in the single neuron (right) is similar to the evoked pattern. Reprinted, with permission, from Tsodyks et al. (1999).

dynamically switching attractor states corresponded closely to orientation maps evoked by visual stimuli. Surprisingly, most states corresponded to maps evoked by either horizontal or vertical gratings.[11] This latter finding might explain why cats, humans, and other mammals recognize horizontal or vertical stimuli better than other orientations. Accordingly to this view, stimuli do not simply induce arbitrary ensemble patterns but rather can bring about any of the finite number of default attractor states. A match between a spontaneous cortical state and features of the input should enhance perception, whereas attractor states far from the preferred state of the input configuration may ignore the input, unless the input can "push" the network into the preferred state of the stimulus. This latter effect is similar to the stimulus-induced phase resetting of an oscillator, described above.

In a conceptually related experiment, David Leopold and Nikos Logothetis at the Max-Planck Institute in Tübingen, Germany, examined the relationship between the spontaneous power fluctuation of the EEG and the fMRI signal in the monkey. The EEG power was evaluated separately in the various frequency bands, and the integrated power variations at the second and tens of seconds scales were used for comparison. As discussed in Cycle 5, such low-frequency fluctuations of the EEG include several interacting rhythms (slow 1 to slow 4) and generate a $1/f$ power-law function extending to the minute scale. The interesting novel finding was that the power variation of the EEG signal often strongly corre-

11. The higher incidence of spontaneous states in the vertical and horizontal attractors can also imply that the functional connectivity, underlying cortical assembly patterns, might be experienced derived, since horizontal and vertical stimuli are more frequent in our surroundings than are other orientations. The issue of experience versus intrinsic mechanisms is quite complex, as indicated by early findings of Blakemore and Van Sluyters (1975) that suggest the visual experience is not necessary for the emergence of orientation maps.

lated with the oxygen extraction fraction, measured by fMRI. As was the case in the voltage-sensitive dye mapping experiments in the cat, the locally measured electrical signal covaried with the fMRI signal from large areas of the cortex, in some cases with nearly the entire brain.[12]

A major caveat of the mapping experiments is that the animals were under deep anesthesia, a state that may have limited relevance to the activity of the drug-free brain. Furthermore, no unit recordings were made in the fMRI experiments. Nevertheless, previous studies in both anesthetized and behaving animals have provided ample evidence for the large-scale changes in neuronal excitability in multiple brain areas associated with the slow EEG power fluctuations.[13] Furthermore, the principle suggested by the experiments under anesthesia should remain the same in the waking brain: the internally generated attractor states in the cortex can bias the brain's ability to extract information from the environment. This principle also follows from the simultaneous feedforward and feedback operations of the cortex, implying that the flow of activity even in primary visual and other sensory areas is inherently multidirectional.[14] If so, spontaneous background activity should exert a major impact on cognitive and motor behavior.

Behavioral Performance Is Affected by Brain State

The attractor dynamics explanation of brain-state–dependent processing can explain the Canadian neurosurgeon Wilder Penfield's celebrated observations in the mid-1950s. He stimulated various sites of the surface of the neocortex of epileptic patients and asked them to narrate their experience. The stimulations evoked dream-like sensations, combining the actual situation and assumed recalled memories. Repeated stimulation of the same cortical site typically produced different experiences, while stimulation of some other sites could evoke the same experience.[15] A possible explanation of the stimulation results is that the stimulation effects were combined with the ongoing trajectories of neuronal activity. This, of course, remains a conjecture since no recordings were available in the human experiments; therefore, the brain-state history dependence hypothesis cannot be verified. A straightforward way to examine the effect of brain state on performance is to examine neuronal activity prior to the occurrence of some cognitive or motor act.

12. Although most physiological measurements were examined in the waking monkey, the EEG power vs. fMRI comparisons were carried out under anesthesia (Leopold et al., 2003). The spontaneous fluctuation of activity and associated fMRI and PET signals prompted Raichle et al. (2001) to question the validity of the widespread "baseline subtraction" method of imaging. Ideally, the baseline should be related to a physiologically well-defined state, rather than just an arbitrary epoch before task manipulations.

13. For a review on the unit discharge variations in slow oscillations in various brain regions, see Penttonen and Buzsáki (2003).

14. Several reviews discuss the highly complex, parallel, and recurrent processing of visual information (Bullier and Nowak, 1995; Schroeder et al., 1998; Lamme and Roelfsema, 2000).

15. Penfield and Jasper (1954).

I have already discussed how the oscillatory phase of population activity can affect motor execution and reaction times in humans. Similar observations are also available in monkeys, where the task sequence was initiated by the monkey rather than the experimenter. By pressing the bar, a diamond or a line appeared on the screen, and correct identification of the shape was rewarded. The power in the 5–25 hertz band in the prefrontal area and the phase coherence in the same frequency band highly correlated with both the amplitude and latency of the evoked potentials recorded in the occipital cortex, as well as with motor response time. These findings support the idea that the state of the prefrontal cortex can prepare sensory areas for more efficient processing.[16]

Similar state-dependent effects have been shown repeatedly for encoding episodic and semantic memories. Memory encoding refers to the hypothetical process that mediate between experience and the formation of a memory trace in the brain of that event. What we remember and what we forget is not a simple decision that we can command ourselves. Various electrophysiological parameters, measured at the time of encoding, have been shown to distinguish between items that are recalled later versus those that are not recalled. The waveforms of item-evoked potentials in the rhinal cortex and hippocampus in human epileptic subjects at the time of encoding reliably predicted whether the item was subsequently recalled or not. Increased transient gamma synchrony between these areas also predicted successful recall.[17] Similar predictive correlations were observed between scalp-recorded theta power at the time of encoding and later recall. Recently, large-scale subdural recordings in humans have provided extensive support for the hypothesis that variation of the ongoing brain states is a key factor in determining successful encoding (figure 10.3). In a series of experiments involving 800 recording sites in a group of patients, a significant number of electrodes showed increases in oscillatory power at the time of encoding of the subsequently recovered items. Sites associated with increased theta oscillations (4–8 hertz) were clustered predominantly in the right parietal-occipital cortices, whereas sites exhibiting increased gamma oscillation power were quite scattered, indicating that power fluctuation of the rhythm in widespread cortical areas can influence processing of external inputs (see also Cycle 12).

These findings in humans echo early observations in rabbits. Rabbits, like lizards, birds, and some other mammals, have a third eyelid, called a nictitating membrane. Any stimulus to the eyeball (e.g., a puff of air) will result in an unconditioned reflex contraction of the translucent nictitating membrane. When the puff of air is consistently preceded by an otherwise neutral signal (e.g., a sound), the animal learns to close the nictitating membrane prior to the occurrence of the unconditioned air puff after a several dozen pairings. A number of external factors, such as the temporal gap between the conditional (sound) and unconditional signals and

16. Liang et al. (2002).

17. Fernandez et al. (1999) and Fell et al. (2001). These observations support previous scalp-recording studies, which showed larger positive components of evoked potentials during verbal encoding of subsequently remembered words than of subsequently forgotten ones (Halgren and Smith, 1987; Paller et al., 1987).

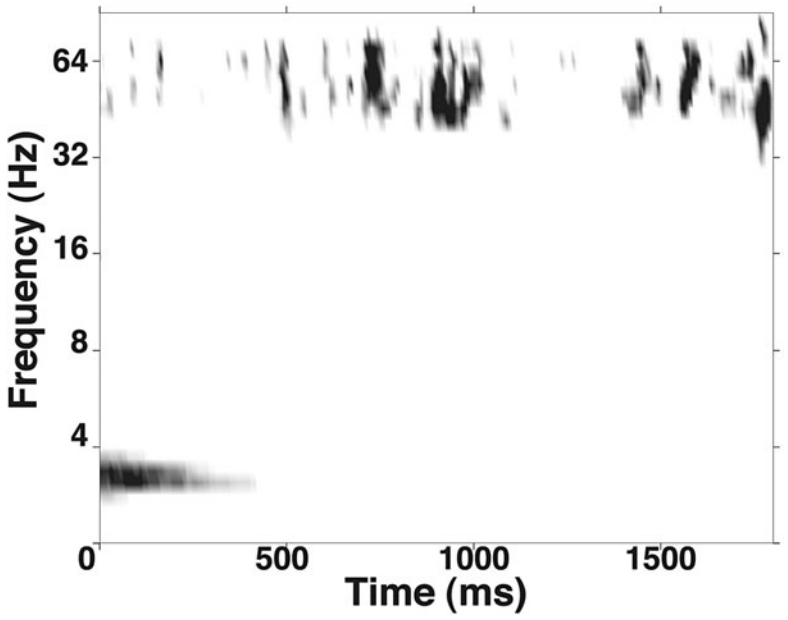

Figure 10.3. Power of gamma frequency oscillation is increased during successful memory encoding. Gray areas in the time–frequency spectrogram (2–96 hertz) illustrate significant increases in oscillatory activity during successful versus unsuccessful encoding. Note increase in gamma-frequency power, centered around 40–80 hertz, for subsequently recalled words first between 500 and 1,000 milliseconds after the word presentation onset (0 milliseconds) and again around 1,500 milliseconds into the encoding epoch. Data were obtained from 91 left-hippocampal electrodes of 15 epileptic patients undergoing invasive monitoring for seizure localization. A similar pattern of increases in gamma power during successful encoding is also visible at a number of cortical regions, including left inferior prefrontal cortex and left temporal lobe. Figure is courtesy of M. Kahana, summarizing the findings of Sederberg et al. (2003).

their strength, affect the speed of learning. However, the state of the rabbit's brain at the time of the arrival of the sound is also a critical variable. The power of hippocampal theta oscillation positively and robustly correlates with the pace of conditioning. Rabbits with no detectable theta in the recording situation require five times more trials to learn the task than do rabbits with the highest power of theta.[18]

Another set of experiments illustrates further that the animal's response to the same physical stimuli depends on the internal brain state. In that experiment, cats were trained to discriminate between two distinct stimuli, so that stimulus A and stimulus B required two different behavioral outcomes (e.g., approach right and left feeder, respectively). After mastering the task, the evoked responses evoked by the two physically different stimuli were quite distinct. When the cat mistakenly

18. Berry and Thompson (1978).

went to the left feeder in response to stimulus A, the evoked-potential responses corresponded to the usual correct responses to stimulus B, congruent with the cat's "belief " about the correctness of the response. Obviously, the "readout from memory" components of the evoked responses reflected the brain's "interpretation" of the signals rather than the physical features of the stimuli.[19]

The above observations in humans and other animals are generally interpreted within the psychological framework of selective attention, reflecting a top-down executive mechanisms associated with gamma and theta oscillations.[20] A logical consequence of this hypothesis is that, for successful encoding, all we have to do is to keep our brains in the optimal state and generate sufficient amounts of theta and gamma oscillations. However, the brain simply does not work this way, at least not for sustained periods. Somehow the hypothetical executor fails to maintain long-term control. One way of "instructing" the key parts of the brain to perform better is to send signals from the body and the environment. We all have experienced the feeling of irresistible fatigue during a long drive. The most efficient way to prevent our brain from falling asleep is by stretching the arms, moving the head, blinking the eyes, deep breaths, fresh air, turning on the radio—in other words, by feeding the brain with peripheral signals. Left without external stimulation, the brain succumbs to its internally programmed oscillations, resulting in fluctuating levels of neural performance. For the same reason, there is no simple way for willfully sustaining attention, perception, memory, or motor output for arbitrarily long periods.

An alternative explanation for the fluctuation of our ability to perceive, learn, and act is that the power of gamma and theta oscillations is not controlled by hypothetical intentionality or an executor but is modulated in time by ongoing slower rhythms. For example, changes of spontaneous firing rates in the noradrenergic locus ceruleus neurons of monkeys are closely correlated with fluctuations in cognitive performance.[21] The released neurotransmitter norepinephrine is known to enhance both theta and gamma oscillations. Another indication of an internal mechanism responsible for the fluctuation of perceptual and motor readiness state is that, in humans, the power variation of scalp-recorded gamma and theta activity shows a $1/f$ power-law scaling behavior.[22] In summary, these obser-

19. See Sutton et al. (1965) and Grastyán et al. (1978).

20. Raghavachari et al. (2001) and Sederberg et al. (2003). Increased gamma power is often interpreted as a physiological correlate of attention (Tiitinen et al., 1993; Engel et al., 2001; Fries et al. (2001a, b). An implicit implication of these findings is that drugs that increase theta and gamma power should improve encoding of memories.

21. For the role of locus ceruleus neurons in affecting cognitive performance, see Usher et al. (1999). Neurons in several subcortical nuclei have been described as showing very large firing rate fluctuations at a slow 1 to slow 4 frequencies (see Penttonen and Buzsáki, 2003). Moruzzi and Magoun (1949) formulated the reticular activating system framework, implicating that bottom-up, nonspecific mechanisms are necessary for maintaining forebrain activity in the waking state. Of course, the investigators at that time were not aware of the numerous neuromodulators that are part of the ascending systems.

22. The exponent of the $1/f^{\alpha}$ relationship is somewhat different for gamma and theta power fluctuation (Linkenkaer-Hansen et al., 2001; Stam and de Bruin, 2004). In agreement with these findings, Başar (1990) was among the first to suggest that EEG activity is best described as quasi-deterministic activity.

vations lend support to the idea that brain-state fluctuations are neither random nor simply controlled by "will-guided" top-down mechanisms.

A sensitive method for examining the influence of self-organized brain patterns on cognitive performance is to present ambiguous figures to subjects. In this case, perceptual shifts are expected to be driven by the variation of brain dynamics in the absence of any changes of environmental inputs. One such well-studied illusionary figure is the Necker tube (see figure 8.7). When confronted with a reversible figure such as this, viewers experience a spontaneously changing percept, alternatively seeing either the bottom or the top of the cube. Since the input remains constant, it is our brain that does the switching by some rules. Switching occurrences can be tracked by asking the subject to press a key each time they perceive a change in the orientation of the cube. The switching intervals often do not reflect a characteristic time scale, which led several investigators to believe that the pattern of alternation was stochastic. However, quantitative analysis of the time series of orientation reversals revealed a $1/f$ function, suggesting a memory effect. These findings echo the scale-free distribution of errors of the syncopation experiments discussed in Cycle 6.

The role of brain-state changes in perceptual switching is further supported by the observation that spontaneous alternations occur only during continuous exposure of ambiguous figures. The perceptual alternation can be slowed or even prevented by periodically removing the figure from view, for example, by frequent blinking. The brief exposures prevent switching during the stimulus presentation and set the context for subsequent perceptions. Manipulations of binocular disparity also affect perceptual stability. High-depth conditions yield less frequent perceptual reversals than do low-depth conditions, supporting the view that the more ambiguous the figure is, the stronger the role of spontaneous brain activity.[23]

Overall, the observations on ambiguous or puzzle figures illustrate that the brain is compelled to interpret and that the interpretation is a combined effect of the physical nature of the input and the temporally evolving spontaneous brain state. Because of the additive contribution of the brain, the behavior of a neuron or local network does not faithfully reflect the physical features of the input. If we want to determine the firing pattern of a cortical neuron, we would need to know the discharge patterns of all connected cells in the immediate vicinity, and preferably at more distant sites, as well. To improve the prediction, we would need to know not only the current state but also the activity that occurred in the prior 100 milliseconds or seconds ago. In short, information about the recent history of all inputs is needed to improve prediction.[24] This historical dependence is what

23. It has long been thought that perceptual switching is a result of some internal brain computation (Attneave, 1971). However, this view was challenged because of the assumed stochastic properties of switching (Fox and Herrmann, 1967). Leopold et al. (2002) found that spontaneous alternation of the percept during continuous exposure to a rotating random-dot sphere showed a characteristic frequency at 0.3 hertz. Aks and Sprott (2003) found scale-free distribution of perceptual switching with the Necker cube.

24. An especially elegant demonstration of such context dependence was demonstrated in a free-recall task using fMRI. Subjects had to memorize a list of items consisting of three distinct categories (faces, locations, objects). In each scan, a large number of brain structures were scanned and their

makes the brain a dynamic system. The structural basis of dynamic behavior may be the multiple parallel loops, which provide feedback at extended temporal scales due to the progressively longer conduction and synaptic delays in longer loops. These feedback loops acting at multiple temporal and spatial scales embody the context dependence of input perturbations.[25] In this framework, context is defined as a set of conditions in which an input is uniquely coupled to an output. It is a sorting mechanism that directs the neuronal representation of the input to the most appropriate circuits on the basis of the input's historical association with the brain's previous responses.

To fully appreciate the consequences of such multilevel interactions, we must monitor changes in multiple related systems (Cycle 12). However, before we can address the complex issues of systems interactions, first we need to explore how long-term memories are formed, because it is the experience of each individual that fundamentally determines how the brain reacts in various situations.

Briefly . . .

The variation of our motor and cognitive abilities is present at multiple time scales, expanding from periods of tens of milliseconds to hours. The brain-state variability to a large extent is internally coordinated even in the waking brain. This internal coordination is not simply "correlated noise" that the brain should overcome and the experimenter must eliminate to reveal the true attitude of the brain to an environmental input. Instead, the time-evolving brain states are an important source of mental operations. The recorded signals may contain more information about the observer's brain than about the signal because the mechanism of perception is an "interpretation" by the neuronal circuits rather than a summation or "binding" of invariant physical features. Precisely what makes the brain a dynamic system is that its current state is, in part, dependent on a prior one. In order to predict the state of a neuronal network, one needs to have access to its recent history. The $1/f$ brain dynamic, as revealed by various global physiological measurements, is often reflected by a similar $1/f$ scale freedom of overt behaviors, such as various mental operations and motor outputs. From this perspective, the neuronal "signal" in response to a given environmental perturbation of the brain state is not an initial condition but, rather, a modification of a perpetually evolving network pattern in the brain's landscape.

BOLD constellations during the study phase were classified according to the categories (see Cycle 4 for a description of the technique). During free recall in the absence of cues, the three category states shifted regularly with a 5- to 10-second periodicity, determining the categories of items to be recalled, and the magnitude of the match predicted what kinds of information the subjects retrieved (Polyn et al., 2006).

25. Although the temporal aspect of state implies context, I provide a more precise neurophysiological definition of context in Cycle 12.

Cycle 11

Oscillations in the "Other Cortex": Navigation in Real and Memory Space

> I've never tried to block out the memories of the past, even though some are painful. . . . Everything you live through helps to make you the person you are now.
>
> —Sophia Loren

Despite its beauty and complex order, the relatively uniformly organized modular neocortex has its limitations. The functions that its mostly locally organized structure supports are tuned mainly to detect orderly relationships in the environment. The perceptions of natural scenes, speech, music, and body image as well as our occasional illusions can be attributed largely to the unique organization of the isocortex. Brains with these features of organization are useful as long as they are embedded in an unchanging environment. However, we live in an ever-changing world, and numerous events relevant to our survival and happiness occur independent of us and often in an idiosyncratic manner. It is impossible to create or even imagine a machine that would be able to detect and store all of the random events and relationships around us. Most of these random events are irrelevant and do not have any personal significance. But some do. Our names, the birthdates of loved ones, and other important family events are our unique experiences, which do not simply unfold by some external rules. Forming and storing of individual experiences create a knowledge base, a unique brain-based context that modifies the way the neocortex processes future sensory experiences and contingencies and affects our actions. The accumulation and persistence of past experiences of the individual, collectively called memory, are responsible for creating individual identity.

The emergence of individuality and personal identity are therefore strongly

linked to mechanisms that enable an animal to recollect the past and modify its future behavior on the basis of these recollections. There is nothing in the physical world that would tell us whether a face is pleasant or repellent to us. The same face may be judged as beautiful or ugly on the basis of the cumulative past experiences of different observers.[1] What are these experiences, and where are they stored?

Experiences stored in the brain are usually divided into two major categories: implicit and explicit. For a psychologist, the term "explicit" or "declarative" means that such experiences have "conscious" recollections and can be declared verbally. They include lifetime episodes unique to an individual, such as your first accepted paper or getting your first grant, or learning arbitrary facts related to the world we live in, such as the distinction between relaxation and harmonic oscillators. These latter factual or semantic memories lack a unique personal link. In contrast, the implicit experience of learning how to walk comfortably in high-heeled shoes or ignoring the annoying sound of the air conditioner in your office does not require that we be aware of the process.[2]

Forming and storing arbitrary episodes require a suitable large storage space with randomly organized connections. By now, we have learned that the six-layer neocortex with its regular modular architectonics and that mostly local wiring is far from ideal for such a task. A large part of the modularly organized neocortex is tuned to extract statistical regularities in the world conveyed by our sensors. But there is another piece of cortex that we have hardly mentioned so far: the "other cortex," or, in our Hellenistic scientific jargon, the allocortex (also called heterotypical cortex), with its variable numbers of layers, unique cell types, and a special wiring plan (figure 11.1). This piece of cortex, as I describe below, contains a large connection space that is ideally built for the construction of episodes and event sequences from arbitrary relations by providing a spatiotemporal context for the information to be deposited.

The speculation about memory space is supported by clinical findings in humans: damage to the hippocampus–entorhinal cortex system results in profound memory problems. In contrast, single-cell research in animals has provided a different perspective, namely, that the hippocampus and associated structures serve spatial navigation. Both of these research lines have coexisted with the extensive work on hippocampal oscillations, but the three research directions have converged only recently. A major goal of this Cycle is to discuss and illustrate how oscillations can link these disparate directions and provide a

1. This is not to deny the importance of species-specific biases even in lately developed species, e.g., the inborn fear of snakes in primates. Nevertheless, in animals with larger and more complex brains, perception and action become progressively modified by individually acquired associations.

2. See Cycle 8, footnote 12, for the major memory categories. Many excellent and easily readable works are available on the taxonomy of memory and about the relationship between the different memory categories and brain structures. Here is my short-list: Tulving (1972, 2002), Squire (1992), Eichenbaum (2002), and Nadel and Moscovitch (1997). For a very readable history of twentieth-century memory research, see Milner et al. (1998).

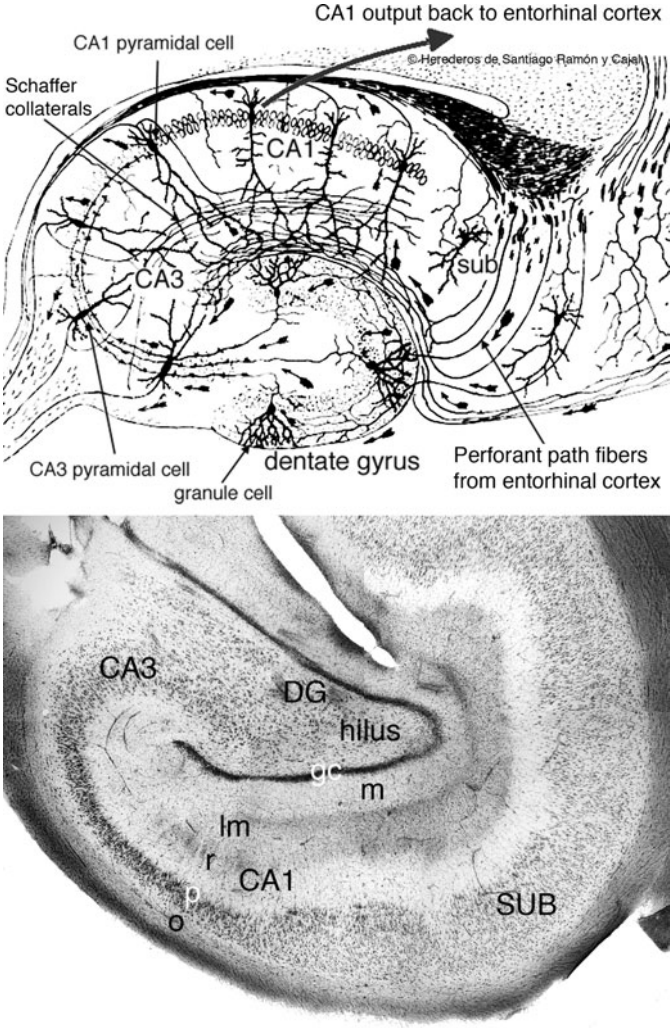

Figure 11.1. Excitatory circuits of the hippocampal formation. Top: Santiago Ramón y Cajal's drawing of the major cell types and their axonal projections in the rodent brain. (Reproduced, with permission from Ramón y Cajal S (1901). The original is figure 41 in Ramón y Cajal (1901) and figure 167 in DeFelipe and Jones (1988). Perforant path fibers from layers 2 and 3 of the entorhinal cortex (not shown) project to the dendrites of dentate granule cells/CA3 pyramidal cells and CA1 pyramidal cells, respectively. The arrow shows one fiber. The parallel running fibers cross the dendrites of granule cells and pyramidal cells. Granule cells project to CA3 pyramidal cells, whose major axon collaterals, also called Schaffer collaterals, innervate CA1 pyramidal cells. Ramón y Cajal believed that the output axons of CA1 pyramidal cells left the hippocampus in the fimbria and traveled to subcortical destinations (see small directional arrows). In reality, the majority of CA1 axons target neurons in the subiculum (sub) and the deep-layer cells of the entorhinal cortex (large arrow). Bottom: Section of the human hippocampus. In contrast to the rodent hippocampus, which extends above the thalamus, the hippocampus in primates assumes a ventral location in the temporal lobe. This is why the position of the layers is reversed compared with the top drawing. o, stratum oriens; p, stratum pyramidale; r, stratum radiatum; lm, stratum lacunosum-moleculare; m, dentate stratum moleculare; gc, granule cell layer. DG, dentate gyrus; SUB, subiculum. Courtesy of Tamás Freund and Zsófia Maglóczky.

coherent picture for the functions of the hippocampal–entorhinal system.[3] To achieve this goal, we need to cover several lines of seemingly independent investigations before we can combine them into a comprehensive, oscillation-based framework.

The Allocortex Is Sandwiched between the Oldest and the Most Recent Brain Parts

The safest way to start speculating about the functions of a structure is to inspect its anatomical organization carefully. The dictum "structure defines function" never fails, although the architecture in itself is hardly ever sufficient to provide all the necessary clues. Nevertheless, knowledge about the nature of neuronal connections provides important constraints and reduces the large degree of freedom of speculation to manageable levels. As discussed in Cycle 2, the brain is essentially a multitude of superimposed and ever-growing loops between the input from the environment and the brain's outputs, the most important of which is movement. The number of superimposed loops in the complex mammalian brain is impossible determine, so perhaps it is useful to reduce the numbers by some rational grouping. Paul McLean at the National Institutes of Health suggested that three gross levels of brain organization are about right.[4] His bottom tier is an interconnected series of structures that are easily recognizable also in premammals; therefore, he uses the term "reptilian brain" or, to sound more scientific, the archipallium (Latin for ancient brain), as a collective name for structures that include the olfactory bulb, brainstem, mesencephalon, cerebellum, and the basal ganglia. On the top of the organization lies the latest and superior mammalian invention, the neopallium, which is more or less equivalent to the thalamoneocortical system. Sandwiched between the "primitive" reptilian brain and the rational new brain lies an intermediate tier, the mesocortex or paleopallium, comprising the structures of the limbic system.[5] According to McLean, these three tiers emerged chronologically during the course of the evolution of animal species from lizards up to *Homo sapiens,* and the sequential order is also recapitulated during ontogenenesis.[6]

3. Focusing on a single topic (i.e., episodic memory) comes at the expense of ignoring numerous other important functions of the allocortex, e.g., emotions, olfaction, and movement control.

4. McLean has published numerous papers on the triune brain since the 1950s, summarized in a comprehensive volume (MacLean, 1990). MacLean did not speak about parallel loops. Instead, he envisioned the three layers as strict hierarchies.

5. Besides the limbic system, the allocortex also contains the olfactory cortex, a sensory area without thalamic connections. The striatum, medial nuclei of the amygdala, and nucleus accumbens are sometimes also labeled as allocortical structures, although they are not considered parts of the limbic system (Graybiel et al., 1994). The olfactory cortex, lateral amygdala, and hippocampal system are collectively referred to as the medial temporal lobe. De Curtis and Paré (2004) provide a concise summary of the structure and functions of rhinal cortices.

6. This tacit assumption may not hold. Starting with Rose (1937), several evolutionary biologists have argued that the mesocortex and especially its key structure, the hippocampus, made its first

The main border between the allocortex (paleopallium) and the overlying neocortex is the rhinal (i.e., nose-related) fissure, a large canyon easily recognizable in most mammalian brains. A common feature of allocortical structures is the violation of the strict six-layer modular arrangement of the isocortex. As is the case for the neocortex, sensory information cannot directly penetrate the structures of the allocortex. Olfactory information arrives most directly by way of a thalamus-like relay station, the olfactory bulb, whereas all other sensory information reaches the allocortex through tortuous paths by way of the neocortex.

Because of the relatively direct access of olfactory information to some allocortical structures, early investigators used the term "rhinencephalon," implying that the dominant function of most allocortical structures was processing olfactory information. The later-introduced term "limbic" system derives from the ringlike arrangement of allocortical structures, including the amygdala, hippocampus, entorhinal cortex, and hypothalamus, that provide a relatively distinct border separating the brainstem from the new cortex.[7] Because many psychological constructs, such as emotions and feelings, boredom and passion, love and hate, attraction and disgust, joy and sadness, are thought to be mammalian inventions, and neither the reptilian brain nor the rational neocortex seemed suitable sites for such functions, these functions were delegated to the limbic system.[8]

These assumptions made perfect sense in light of the known anatomy of the limbic system 40 or so years ago. According to the anatomical knowledge at that time, the main input to the limbic system is the neocortex. Virtually all neocortical regions project to the perirhinal and entorhinal cortices, and the neocortical information is funneled to the hippocampus by these structures. Thus, according to the brain hierarchy formula, the hippocampus is the ultimate association structure, receiving the highest order neuronal information (see figure 2.6). So the key question is: what happens to the information funneled to the hippocampus? According to the main anatomical authority of the times, Santiago Ramón y Cajal, the hippocampus-processed information is sent *down* to the reptilian brain (figure 11.1).[9] In support of this neopallium–paleopallium–archipallium funneling traffic, anatomical and lesion studies also indicated that the hippocampus and amygdala are critical in the control of hypothalamic endocrine and autonomic function.

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appearance in mammals, virtually simultaneously with the emergence of the isocortex. On the other hand, birds also have a structure analogous to the hippocampus, with potentially similar functions as in mammals but no granule cells (e.g., Doupe, 1994).

7. In Latin, *limbus* means a surrounding ring. The French neurologist Paul Broca introduced the term *la grand lobe limbique* in 1878. Papez (1937) went further by postulating that emotions reverberate in the ring, often referred to as the Papez circle.

8. The pivotal role of some amygdaloid nuclei in emotions led to the still oft-used term "emotional brain." The best-written works on this subject are Damasio (1995) and LeDoux (1996). Endre Grastyán attributed ludic (playful) behaviors, a mammalian specialty, to the hippocampo-amygdaloid system and explained their regression during ontogenetic development by the increasing dominance of the rational neocortex (personal communication).

9. Ramón y Cajal (1909, 1911).

Putting all of the available pieces of the puzzle together, the following picture emerged: the results of the rational neocortical computation are transferred to the allocortex; after proper evaluation of the emotional content by limbic structures, the hippocampal and amygdalar outputs instruct the skeletal and autonomic effectors to fight or flight, increase or decrease heart rate and blood pressure, and to mobilize stress and other hormones.[10]

But even giants can make (small) mistakes. A few decades after Ramón y Cajal outlined the direction of the main hippocampal output, it was discovered that the subcortical projection of the hippocampus is not the most significant output projection. Instead, the principal hippocampal efferents return to the subicular complex and to the deep layers of the entorhinal cortex, from where the information is routed back to the neocortex. Thus, the principal direction of neocortex–paleocortex traffic is not downward to the archipallium but upward to the neocortex. The organization is not a simple feedforward hierarchy but a recurrent loop. Of course, finding a massive return path from the hippocampus to the entorhinal cortex does not invalidate the importance of the hippocampal and subicular output to downstream projections (fornix) and the associated physiological functions associated with this output.

Ignoring the anatomical knowledge of the times, the psychologist Brenda Milner and the neurosurgeon William Scoville concluded in the late 1950s that the hippocampus was related to memory functions. Studying the now famous patient H.M. and several related cases with bilateral surgical removal of the hippocampus and some surrounding structures, they consistently observed that acquisition of new episodic-declarative knowledge was no longer possible in these people. Nevertheless, these patients retained and effectively used most of their experiences prior to the surgery.[11]

Memories are useful only if they can be retrieved. Obviously, if the sole outputs of the hippocampus were the few efferent fibers projecting downstream into the fornix bundle, it is hard to see how the neocortex could get quickly informed about previous experiences, that is, retrieve memories. The new anatomical picture that has emerged provided a different insight. The main outputs of the hippocampal formation and the amygdala are the same as their inputs: the neocortex. These structures can therefore be viewed as "appendages" of the large neocortical mantle with bidirectional traffic. From this gross anatomical vantage point, we can ask a critical question: what functions can a structure perform whose main outputs are the same as its inputs? Not many. The only thing it can do reasonably well is modify the inputs. In light of the clinical observations of Milner and Scoville, this is good news, however. The paleocortical output may

10. See the pioneering studies by Gorski (1974) and for recent reviews: Sapolsky (1998) and McEwen and Lasley (2002).

11. Scoville and Milner (1957). For the debate about memory and other functions of the limbic system, see Isaacson (1994) and Vanderwolf (2003). Swanson and Cowan (1977) were the first anatomists to emphasize that the main hippocampofugal path is projected to back to the entorhinal cortex.

assist in modifying the neocortical circuits. The combination of the knowledge gleaned from the human surgical cases and the new anatomical information obtained in animals initiated an entirely different direction for limbic system research: memory.[12]

The Hippocampus Is a Giant Cortical Module

Allocortical structures have a different anatomical organization than does the isocortex. In most allocortical areas, layer 4 is absent, reflecting the lack of a major thalamic input. In other cases, such as the lateral amygdala, the regular cytoarchitectonics is missing. But what makes the paleocortex qualitatively so different from the neocortex is the hippocampal formation.[13] Like the isocortex, most paleocortical structures are constructed from pyramidal cells and GABAergic interneurons, although their layer and wiring organizations vary substantially from the regular isocortical modules.[14] The hippocampal dentate gyrus has a radically different cell type, called granule cells, with fundamentally different features from pyramidal neurons. Because of their qualitatively different nature, there is reason to believe that the unusual properties of granule cells hold the key to a comprehensive understanding of hippocampal function.[15] Paradoxically, it is the dentate gyrus component of the hippocampus whose functions we understand the least.

The hippocampus is a one-layer cortex, according to anatomical textbooks, but that depends on how one looks at it. Indeed, if one unfolds the tooth-shaped dentate gyrus and the C-shaped hippocampus proper, also called cornu ammonis (CA or Ammon's horn), a large sheet with a single layer of granule cells and pyramidal

12. The rest of the discussion focuses on the hippocampal system. Another key limbic structure, the amygdala, is neglected, mainly because excellent books have been written on the amygdala and its role in emotions (Damasio, 1995; LeDoux, 1996). For a review of the role of oscillations in amygdala function, see Paré et al. (2002). Since I have very little to add to their views, I do not repeat the discussion here. For the anatomical classification and connections of the various nuclei of the amygdaloid complex, read the comprehensive reviews by Pitkanen et al. (2000) and Swanson (2000). For a detailed discussion of the entorhinal–perirhinal structures, see Suzuki and Amaral (2004), and for a general overview of the paleocortex, I suggest Pigache (1970).

13. My anatomical discussion here is strongly biased toward the hippocampus, because this is the structure that, to date, provides the best understanding of the functional roles of oscillations.

14. The term "layer" is often used differently by anatomists and computational modelers. For the latter, the layer refers to a group of parallel computational units. In anatomy, the Latin *stratum* refers to vertically separable organization, e.g., dendritic and somatic layers, or distinct inputs from various sources.

15. My hunch about the critical role of granule cells was based on the hypothesis that the major role of granule cells is to alter the synaptic weights in the CA3 recurrent matrix during learning (Buzsáki, 1989). Granule cells are special in other contexts as well. They co-release both glutamate and GABA (Sloviter et al., 1996). Most granule cells in rats and humans appear after birth and continue to divide throughout life (Gage, 2002; Gage et al., 1998), and they cannot survive in the absence of circulating steroids (Sloviter et al., 1989).

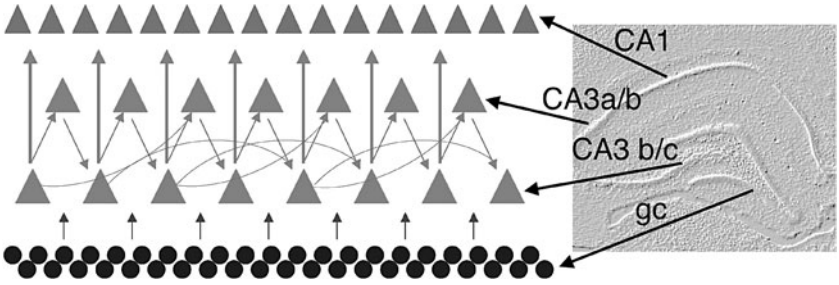

Figure 11.2 The entire hippocampus can be conceived as a single giant cortical column. The bottom-layer granule cells (gc) disperse ("orthogonalize") input information for the second-layer CA3b/c neuron, which project mainly to CA1 but also to the largely recurrent CA3a/b population. Mossy cells in the hilus (not shown), which provide excitatory feedback to large numbers of granule cells, can also be conceived as a separate layer.

cells is obtained.[16] But if one looks at connectivity and disregards size, the resemblance of the hippocampus to a neocortical module is hard to miss (figure 11.2). One important entry point to the hippocampus is the granule cells of the dentate gyrus. The axon terminals of granule cells excite about half of the hippocampal pyramidal cells; these reside in the CA3 region. The CA3 region is actually two layers with a continuous transition. Pyramidal cells in the so-called hilar or portal area engulfed by the granule cells send their main collaterals to the CA1 pyramidal cells.[17] The remaining CA3 and CA2 neurons compose a strongly recursive network. Instead of transferring the information quickly to the output CA1 neurons, they have very extensive recurrent collaterals, contacting their peers locally and distantly, including those in the hilar region, in addition to contacting CA1 pyramidal cells and even reaching back to the granule cells.[18] Viewed from this perspective, this organization is somewhat analogous to the flow of information in the neocortical layer 4 (think granule cells), layer 3 (hilar CA3), layer 2 (CA1), and layer 5 (recursive CA3 neurons) excitatory feedforward structure. The major difference between the neocortical and hippocampal organizations lies mainly in the manner in which the two systems grew during the course of the mammalian

16. The term "hippocampus," or seahorse, was introduced by the Italian anatomist Giulio Cesare Aranzi because of the macroscopic similarity in appearance of the human hippocampus and this sea creature, with the uncus as the head and the thin curved posterior part as its tail.

17. The thick main conduit axons, curving from the CA3 to CA1 stratum radiatum, are called Schaffer collaterals after the Hungarian anatomist-neurologist Károly (Karl) Schaffer (1892).

18. This CA3–granule cell back-projection is very sparse in the dorsal hippocampus but quite significant in the ventral third in the rat (Li et al., 1994), a hippocampal part analogous to the uncus in primates. Although the CA3 neurons have extensive axonal arbors in all parts of the structure, there are several important anatomical, physiological, and pathological differences between the dorsal and ventral (uncal) parts of the hippocampus. Some of the striking functional differences between the dorsal and ventral (tail body vs. uncus in primates) parts of the hippocampus may derive from their inputs, rather than from differences in internal connectivity. Despite these differences, the concept of large synaptic space in the hippocampus prevails.

evolution. The small-world-like organization allows neocortical growth virtually infinitely, constrained only by the axon conduction velocities and the long-range "shortcuts" necessary to keep the synaptic path lengths in the neocortex short. Evolution of the hippocampal formation follows a different rule. The hippocampus grows as a single large multilayer space.[19] The evolutionary advantage of such an architectural solution is the creation of a giant random connection space, a requisite for combining arbitrary information.[20] The main limitation on the structural growth of the hippocampus is the slow conduction velocities of axons. Indeed, the numbers of neurons in the hippocampus increased only 10- to 20-fold from rat to human, whereas the neocortex expanded by several orders of magnitude during the mammalian evolution. Apart from size and cell numbers, the gross appearance and the microscopic connectivity of the hippocampus in various species are strikingly similar.

What is discussed in Cycle 2 about the brain's loops in general is especially true at the level of the hippocampus. Getting from one neuron to anywhere else is possible by multiple paths, through just one synapse or using as many as 10 steps (figure 11.3). Integration of the return path from the short and long loops depends on the available time windows. Such divergent and convergent reverberating circuits can serve various functions, including error correction, pattern completion, amplification, and temporary storage.

The Hippocampus Is the Neocortex's Librarian

How big is the available "random space" in the hippocampus? We set out to study this important question by labeling single neurons in the intact rat brain and reconstructing the entirety of their axon collaterals and synaptic contacts in three-dimensional space. Here are some useful numbers from the rat. The axon length of a single CA3 pyramidal cell varies from 150 to 400 millimeters, establishing between 25,000 and 50,000 synapses within the same hippocampus and about half as many in the contralateral hippocampus. Because there are approximately 200,000 CA3 pyramidal neurons in each hemisphere, this translates to a total of 40 kilometers of axon collaterals and an estimated 5–10 billion synaptic contacts in each hemisphere (figure 11.4).[21] This incredible wiring matrix is squeezed into the rat hippocampal volume, which is approximately the size of a small bean. Importantly,

19. Because the hippocampus is among the best-characterized networks in terms of anatomy and physiology, understanding its operations has considerable heuristic significance in understanding systems operation in general. It has to be kept in mind, though, that studying the hippocampus in isolation is equivalent to studying an isolated neocortical module.

20. Random access memory (RAM) in the digital computers is a useful metaphor to conceptualize the recursive system of CA3 neurons (e.g., Marr, 1971; McNaughton and Morris, 1987; Kanerva, 1988), but there several differences, as pointed out below.

21. Tamamaki et al. (1988) and Li et al. (1994). See also Ishizuka et al. (1990), Amaral (1993), and Amaral and Witter (1989).

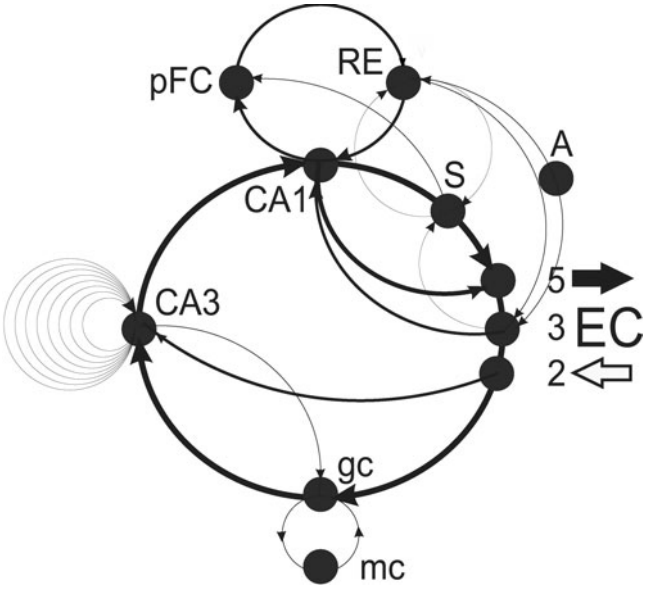

Figure 11.3. Multiple excitatory glutamatergic loops in the hippocampal formation and associated structures. The long loop connecting the layer 2 entorhinal cortex (EC), granule cells (gc), CA3, CA1, and subiculum (S) back to the layer 5 entorhinal cortex is supplemented by multiple shortcuts and superimposed loops. The shortest loop between the entorhinal cortex and hippocampus is the path from the layer 3 entorhinal cortex to CA1 and back to the layer 5 entorhinal cortex. Excitatory traffic in the multiple loops is controlled by a large family of interneurons (see Cycle 2), whose connections are not looplike. mc, mossy cells of the hilus; A, amygdala; RE, nucleus reuniens of thalamus; pFC prefrontal, anterior cingulate cortex.

the distribution is spatially widespread, such that the axon arbor of a single cell covers as much as two-thirds of the longitudinal axis of the hippocampus. Unlike neocortical neurons, hippocampal pyramidal cells do not necessarily prefer their neighbors, and a given CA3 neuron may contact its neighbors with approximately the same probability as some distant peers. The distribution of the contacts in the recursive CA3–CA3 and the feedforward CA3–CA1 projections is reminiscent of a random graph, with 2–5 percent synaptic connection probability.[22] No comparable data are available from other species, but based on the size and numbers of neurons and the volume of the human hippocampus, it is expected that the connection probability of hippocampal cells in our brain is similar to that in the rat. Because extrahippocampal afferents, including the most prominent excitatory entorhinal cortical input, represent less than 10 percent of all synapses, the

22. Connection probability has never been measured quantitatively but is inferred mostly from simultaneous recording from neuron pairs. Approximately 1 in 20–50 pairs shows physiologically demonstrated monosynaptic connections (Miles and Wong, 1986).

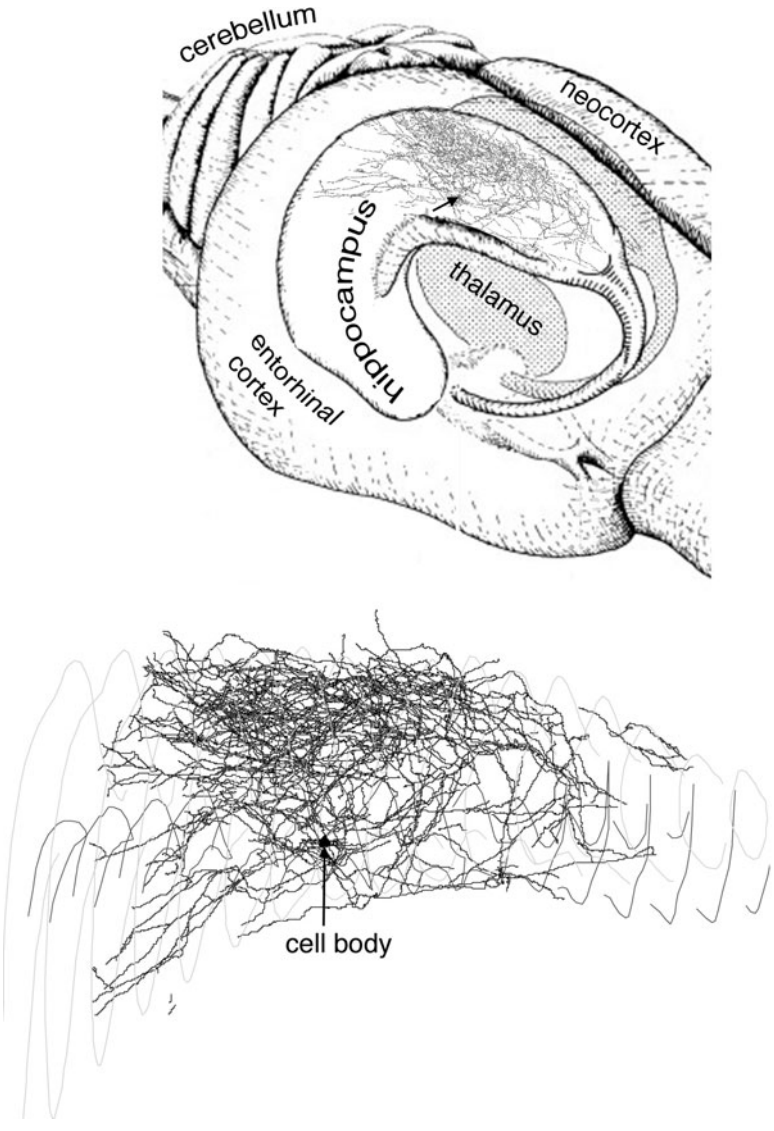

Figure 11.4. The recurrent and CA1-bound collaterals of the CA3 pyramidal cells provide a large three-dimensional random synaptic space in the hippocampus. Top: Collaterals of a single CA3b pyramidal neuron filled *in vivo*. Arrow points to the cell body. Bottom: Higher resolution of the axon collateral distribution. Nearby and distant neurons may be contacted with a similar degree of probability by the collaterals. This single cell had more than 60,000 estimated synaptic boutons. L. Wittner and G. Buzsáki (unpublished observations).

hippocampus can be viewed as a single, supersized cortical module with largely random connections.

Ten billion synapses is not an astronomical figure, especially if one compares it to the number of connections in the human neocortex. However, the hippocampus, being a single giant cortical module, is a vast searchable multidimensional space. To understand the significance of this organization, think of the neocortex as a huge library and the hippocampus as its librarian. An ideal library not only contains most books ever written but also allows speedy and accurate access to any volume. Unfortunately, there is no ideal library, man-made or biological. The more books are accumulated in the library, the higher the overlap among authors' names, titles, and content. Searching for an item in such a colossal library can become a nightmare. Finding the book *Sparse Distributed Memory* by Pentti Kanerva is straightforward because of the explicit key words one can supply. But try, for example, to find the book that you can only remember begins with an episode about some Eastern European journalist who never took any notes at the editorial meetings because he remembered all facts including complex projection numbers. With this little fragmentary information, your search might be hopeless in a real library. Even after typing in multiple combinations of numerous key words that you may remember, the Internet search engine Google may give you a million choices, out of which perhaps only one is relevant. However, if you ask your educated librarian, chances are that she would tell you right away that the book you are desperately looking for is Aleksandr Romanovich Luria's little book about a vast memory.[23] The reason for such a huge difference in search efficiency is that your librarian has a hippocampus, whereas Google does not. Thanks to the hippocampus, humans are very efficient at storing and remembering episodes and recovering them from fragments.[24] How do we do that?

23. When I first read Luria's "little book" (1987; published in Russian in 1968), I thought it was a fiction. In reality, it is about Solomon Shereshevskii's boundless memory capacity, a mnemonist who could remember chains of numbers up to 70 digits forward or backward and could not forget them. For most of us, storing and retrieving numbers of arbitrary compilation accurately is difficult because there is nothing unique about sequences of numbers. However, Shereshevskii had synesthetic memory, which can be conceived of as a multidimensional hologram. Instead of remembering meaningless digits, he chunked them and created episodes by blending all of his senses so that the number sequences acquired sound, pictorial, smell, and even taste features. The multimodality episodes became unique personal experiences that could be recreated from small fragments. This came not without costs, though, to the owner of this exceptional quality. Although Shereshevskii was a shy person, he was aware of his exceptional ability and hoped to discover something extraordinary. It did not happen. He had difficulty in recognizing people and reading their emotions from their facial expressions, a skill most of us perform automatically. His difficulty in forming explicit semantic memories may perhaps explain his extraordinary episodic memory. Unfortunately, no histological information is available about his brain.

24. The origin of these views can be traced back to Hirsh (1974) and Teyler and DiScenna (1985), who considered the hippocampus to be a context-indexing device. Episodic memory in its widest definition reflects a unique spatiotemporal trajectory of events. An everyday example of episodic memory is a free recall of particular events. A list of items presented together in a particular temporal context (e.g., a list of arbitrary words or objects) is another example. Damage to the medial temporal cortex, involving the hippocampal–entorhinal area, severely compromises recollection of episodes (Vargha-Khadem et al., 1997; Squire and Zola, 1998; Tulving, 2002).

Search Strategy in an Autoassociator

Let's begin with some theoretical speculation. The computational properties of recursive organization, such as the extensive CA3 recurrent system, meet the requirements of an "autoassociator." By its computational definition, an autoassociator is a self-correcting network that can recreate a previously stored pattern that most closely resembles the current input pattern, even if it is only a fragment of the stored version. Give the autoassociative network part of the content, and it returns the whole. The performance of an associative network is characterized by its memory capacity and content addressability. As the library analogy above implies, these two requirements compete with each other, because storage space is finite and speed is limited. Memory capacity is easy to define: the maximum number of patterns that can be stored and correctly retrieved. Content addressability is a technical term that refers to an ability to recall a whole episode from a retrieval cue consisting of only a small part of the original information.[25]

Finding a book in a library may require an exhaustive search, meaning that every book should be checked, unless the library is organized, in which case some key words can drastically simplify the search. The most efficient method of search depends on the organization of the system. The extensive axon arbors of the CA3 pyramidal cells indicate that the probability of connecting to nearby or distant CA3 neurons is approximately the same.[26] As discussed in Cycle 2, systems with similar "peer-to-peer" contact probabilities can be treated as random graphs. The concept of a random graph implies that one can walk from any neuron to any other neuron along the calculated shortest possible synaptic path, much like one can walk in an unobstructed field from any one place to any other place. Construction of a full random graph from 200,000 CA3 pyramidal cells would require only 15–20 divergent connections from each cell. However, going from any neuron to any other neuron may require an excessively large number of steps (i.e., long synaptic path length, as referred to in Cycle 2). The theoretical minimum of 10–15 connections is in stark contrast to the 10,000–20,000 synapses that an average CA3 pyramidal cell establishes with its peers. With this large divergence, in principle, activity can jump from any neuron to any other through just two synapses. Furthermore, the

25. In autoassociative attractor networks, the maximum number of stored memories is limited by the decimal order of the number of converging synapses on a single cell from other cells. If memories are stored by static anatomical connections only, the upper limit of the number of memories that can be stored in the rat hippocampus would be tens of thousands, and the storage capacity may not increase much more as we go from rat to human (Amit, 1989; Rolls and Treves, 1997; for a synopsis, see Rolls, 1996). These ideas have their roots in early modeling attempts (Marr, 1971; Kohonen, 1984; Kaverna, 1988; Maas and Bishop, 1999). For a comprehensive description of autoassociative networks, see McLeod et al. (1998) and Kanerva (1988).

26. Strictly speaking, this is not quite true. The axon tree of a single CA3 pyramidal cell covers up to two-thirds of the hippocampal volume. Nevertheless, each neuron has some spatial target preference, and there are differences between axon arbors of pyramidal cells in the dorsal and ventral hippocampus (Li et al., 1994). Despite this anisotropy, the random graph analogy of the CA3 system is valid. Adjacent neurons have the same probability of representing overlapping parts of the environment as do spatially distant cells (O'Keefe and Nadel, 1978; Redish et al., 2001; but see Hampson et al., 1999).

large divergence implies that the number of possible routes between any randomly chosen start and goal cell is a truly galactic figure. Nevertheless, no matter how impressive this figure is, we do not get far with such anatomical reasoning alone, because synapses between pyramidal cells are weak, and the discharge of a single starter cell will not be able to fire any of its target peers. Yet, only discharging neurons can be used for encoding and retrieving memories.[27] Furthermore, the strength of the synapses among neurons is highly variable. In other words, not all routes are equal. Finally, the CA3 recurrent graph is directed because connections between cell pairs are rarely reciprocal. Without speculating further, we can register that the CA3 autoassociator and the CA3–CA1 synaptic matrix represent a strongly connected, directed, and weighted graph.[28] This arrangement simplifies how activity can spread in the recursive network. Instead of spreading excitation in any direction randomly, the trajectory of sequentially spiking neurons in the hippocampal space is determined by two factors only: the synaptic weights among neurons and the state of local inhibition. When activity arrives at a bifurcation choice, it will progress along the path with the stronger synapses and least inhibition, i.e., toward to path of the least resistance (figure 11.5).[29]

Precise anatomical data and computational modeling have provided useful guidelines for the assessment of the storage capacity and content addressability of real networks. Several caveats remain, however. The first issue is a safe coding format of the trace. The recommended computational solution is a sparse and distributed memory. "Sparse" representation means that only a fraction of the trace is represented at one physical storage location. Each synapse can store only one fact about the environment or the history of the brain's owner. At the same time, the memory is distributed over a large space. It is a bit like fixing a dozen locks on the same door and hiding the respective keys at different locations, with each location providing a clue about the next location. The anatomy of the hippocampus meets the requirements of sparse representation. Unlike in primary sensory cortices, cell assemblies in the hippocampus, representing the same information, consist of neurons that are distributed virtually randomly over the entire CA3–CA1 regions.[30] Spreading memory traces in a large coding space reduces overlaps among the stored patterns.[31]

27. Encoding is thought of as a neuronal process involved in transforming external events and internal thoughts into both temporary and long-lasting neural representations. This process can take place irrespective of retrieving or reusing that representation.

28. (Muller et al., 1996b). See the extended discussion on the autoassociative graph below.

29. Of course, activity can spread in multiple directions if postsynaptic targets respond with spikes and converge occasionally, generating a manifold trajectory. The number of possible trajectories and, consequently, the number of episodes, represented by sequential activation of cell assemblies, are practically unlimited.

30. The best illustration of sparsely distributed representation is the "place" cells in the hippocampus (O'Keefe and Dostrovsky, 1971). The size of the place fields increases systematically, however, in the septotemporal axis (Jung et al., 1994), and cell assemblies are formed from spatially randomly distributed neurons (Harris et al., 2003).

31. In the brain, members of the spatially distributed cell assembly might be brought together by Hebbian plasticity, discussed further below.

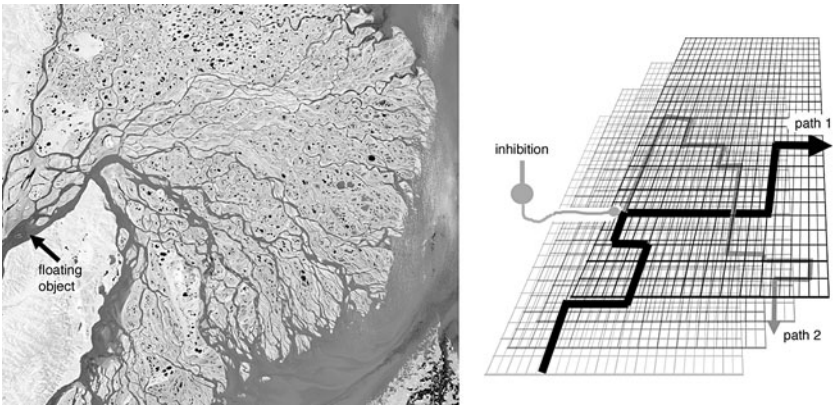

Figure 11.5. Activity spreads along the path of least resistance. Left: A floating object in the delta of the Lena River will follow the path of fastest water flow at each junction. Right: Spread of neuronal activity in a multidimensional grid space, such as the CA3–CA1 network, is determined by two factors: the synaptic strengths between neurons and momentary inhibition. Inhibition at any junction can instantaneously divert the trajectory (path) of activity. The numbers of possible trajectories are high.

Distribution of the input in the large space of the autoassociator requires a special mechanism, and this is where granule cells become critical. Each superficial entorhinal neuron receives inputs from large neocortical areas. In turn, an estimated 50,000 layer 2 stellate cells send inputs to 1,000,000 granule cells, each of which is a recipient of inputs from approximately 10,000 converging entorhinal neurons. Viewed differently, a single entorhinal stellate cell disperses its information to 20 times more granule cells.[32] The goal of this arithmetic exercise is to contrast the large fan-out in the neocortex–entorhinal cortex–granule cell axis with the exceptionally low divergence and convergence of the granule cell projections to the CA3 recurrent system. An average granule cell contacts only 20 CA3 pyramidal cells, a mere 0.1 percent of the possible targets. Because of this low divergence, fewer than 50 granule cells converge on a single pyramidal cell.

As expected from these anatomical figures, many inputs must converge on a granule cell to discharge it, but a fundamentally different mechanism is needed for the granule cell to make itself heard. The unique solution is a giant, so-called "mossy" synapse, placed strategically close to the cell body (figure 11.6). This giant synapse contains multiple transmitter release sites, and under the right conditions a single granule cell is sufficient to discharge its target neurons, as Darrell

32. Tamamaki and Nojyo (1993) filled a single layer 2 neuron *in vivo.* Its enormous axon cloud in the molecular layer of the dentate gyrus and CA3 stratum lacunosum-moleculare illustrated the large fan-out of the entorhinal input. Even if the numbers of neurons that project to the dentate gyrus increase as the brain grows, the divergence still remains respectable.

Henze has shown it in my laboratory.[33] With the help of the granule cells, the input to be memorized can be dispersed into the large space of the CA3 recursive system,[34] at least in the proposed models.

How to Study the Mechanisms of Explicit Memory in Animals?

A major conceptual difficulty of studying the mechanism of memory storage involves the exclusive nature of memory definition. Episodic memory is claimed to be uniquely human, a mental travel back in time that endows the individual with the capacity to reference personal experiences in the context of both time and space. It is these life-long experiences, representing unique events through space-time, that give rise to the feeling of the self and are the sources of individuality.[35] The singular episodes can reemerge through the process of free recall. Semantic knowledge, on the other hand, is largely a context-free form of information. It is the "meaning" of things. Against this background, how are we expected to work out physiological mechanisms of declarative memories in animals simpler than humans?

Luckily, experimental psychology provides some clues about the internal organization of memories. These include the principles of contiguity and temporal asymmetry, studied extensively by Michael Kahana at Brandeis University in Waltham, Massachusetts. The principle of contiguity refers to the observation that subsequent recall of an item is facilitated by the presentation or recall of another item that was presented close in time to the item just recalled. The related principle, temporal asymmetry, is based on another well-known fact: forward associations are stronger than backward associations. If "desk, flower, can, bird, and lamp" were items in the middle of a list to be memorized, and if one recalled "can," the next most likely item to be recalled is "bird." In other words, the item

33. The mossy terminal is the largest cortical bouton and one of the most complex axon terminals in the mammalian brain (Chicurel and Harris, 1992). A comparably effective synapse is the calyx of Held in the auditory brainstem (Habets and Borst, 2005). Granule cells target a disproportionally larger percentage of interneurons than they do pyramidal cells, perhaps to compensate for the strong effect of the mossy terminal (Acsády et al., 1998). The postsynaptic membrane of the mossy terminal does not contain NMDA receptors, and long-term potentiation of the synapse is brought about largely by presynaptic mechanisms (see Henze et al., 2000b). The synapse is extremely sensitive to frequency potentiation, which is the main reason why fast trains of spikes in a single granule cell can discharge its targets (Henze et al., 2002). The frequency potentiation produces activity-dependent delays in CA3 discharges, and these "delay lines" can be exploited for temporal deconvolution of decorrelated neocortical inputs (Lõrincz and Buzsáki, 2000).

34. In computation jargon, the dispersion process is called "orthogonalization," a process that reduces the similarity input patterns, thereby facilitating their unique storage and selective retrieval (Treves and Rolls, 1994; O'Reilly and McClelland, 1994; Lõrincz and Buzsáki, 2000).

35. Tulving (1972, 2002). According to Suddendorf and Corballis (1997), the ability to travel mentally in time constitutes a discontinuity between humans and other animals.

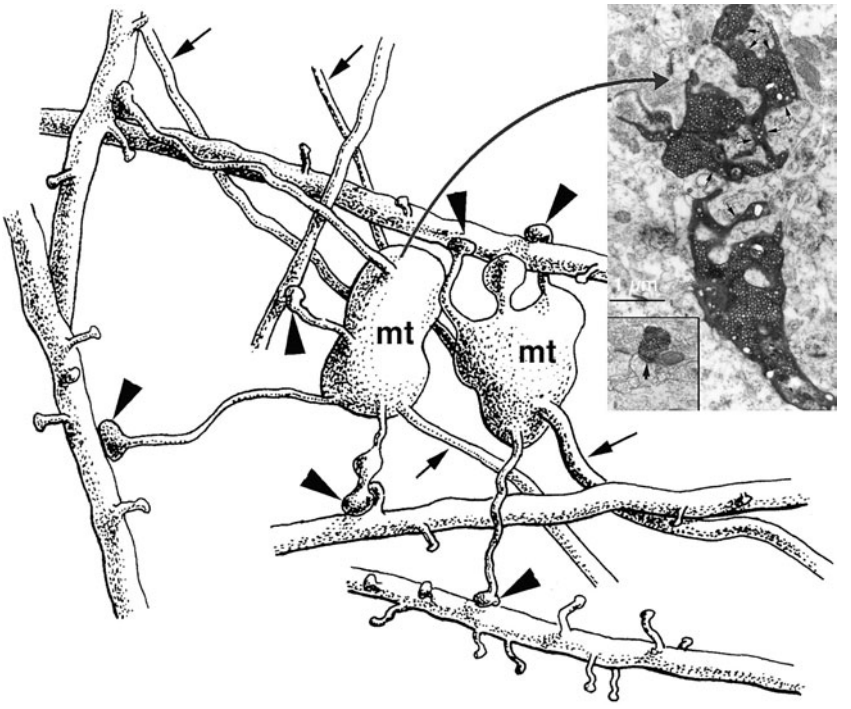

Figure 11.6. Granule cells communicate with their limited number of principal-cell targets via giant boutons (also called mossy terminals, mt) and a larger number of interneurons via filopodial extensions (arrowheads).Arrows, mossy fiber axons of granule cells. Inset: Electron microscopic appearance of the mossy terminal at approximately the same magnification as shown in the cartoon. The large size of the mossy terminal can be appreciated by comparing it with a "regular-sized" excitatory terminal of a CA3 pyramidal cell (small inset, lower left corner). Reprinted, with permission, from Acsády et al. (1998).

to be recalled from the middle of an episode tends to come from nearby serial positions. Furthermore, from the choice of nearby neighbors, the item in the forward direction is twice as likely to be recalled as the item in the backward direction. In essence, recall of a fragment of the episode recreates the temporal context of the episode, and the temporal context facilitates sequential free recall.[36]

Now we have some principles that can guide neurophysiological research in animals. Whatever shape or form a neurophysiological model of episodic memory takes, it must be compatible with these general guidelines and constrained by the unique structural organization of the hippocampal system. As briefly mentioned above, a model cannot be based on anatomical data only. The *potential* of

36. The principles of temporal contiguity and asymmetry are described in Kahana (1996). The "temporal context model" of episodic memory (Howard and Kahana, 2002; Howard et al., 2005) is essentially a recurrent autoassociator in which the previous state of the network contributes to the next. See also Raaijmakers and Shiffrin (1981).

a large searchable space does not tell us how the search is done. For example, once the entire system is searched, what prevents the propagation of activity into an infinite loop? In abstract models, relaxation to an attractor is the usual solution. I suggest that, in the hippocampus, periodic inhibition in the form of theta-frequency oscillation is the solution. However, before we can discuss how episodic memory is carried by the ensemble actions of neurons, we must navigate through 50 years of research on single cells and hippocampal rhythms. These latter two lines of inquiry have progressed relatively independently and often in conflict with research on memory.

Navigation in Two-Dimensional Space

There are various methods of getting from place to place. Christopher Columbus used a method called "dead" (originally called "deduced") reckoning in his voyages in the Mediterranean Sea and to America (figure 11.7). We know this because the dead-reckoning method depends upon continuous measurements of course and distance sailed from some known port, and this method is exactly what Columbus's detailed logs reflect.[37] Course was measured by a magnetic compass. For the calculation of *distance,* the navigator multiplied the speed of the vessel by the time traveled. *Speed* calibration was simple. The pilot threw a piece of flotsam over the side of the ship and started a rhythmic chant when the flotsam passed a mark on the side of the ship and stopped chanting when it passed another mark at a known distance from the first. Remembering the last syllable reached in the chant, the speed was calculated. The total *time* elapsed leaving land was determined by the number of turns of the hourglass or by subsequently developed, more sophisticated clocks. The *direction* of navigation was assisted by a magnetic compass, a key navigation instrument in continuous use in Europe since the twelfth century. At the end of the day, the estimated course and total distance were transferred to a navigation chart and compared to the predicted position of the goal (if known). Estimation of distance by dead reckoning works poorly on long journeys. With an inaccurate chronometer and imprecise instruments to update or recalibrate the boat's position, the errors accumulate over time. On the positive side, the dead-reckoning method does not require visible landmarks and, in principle, works just the same in complete darkness. It was good enough for Columbus to discover the New World.

Reliance of landmarks or celestial bodies is not critical in the Mediterranean Sea, where the latitude is roughly the same wherever you are. However, when Portuguese sailors began their long voyages along the north-south coast of Africa, they soon learned that dead reckoning, without recalibration of the ship's position,

37. The original logs were lost, but the Italian translation by Fernando Colon (1571/1959) survived. For a recent evaluation of Columbus's navigation method, see Pickering (1996). Navigating with the help of a global positioning system (GPS) is essentially instructed dead reckoning, but the routes to the goal are determined by a precise map.

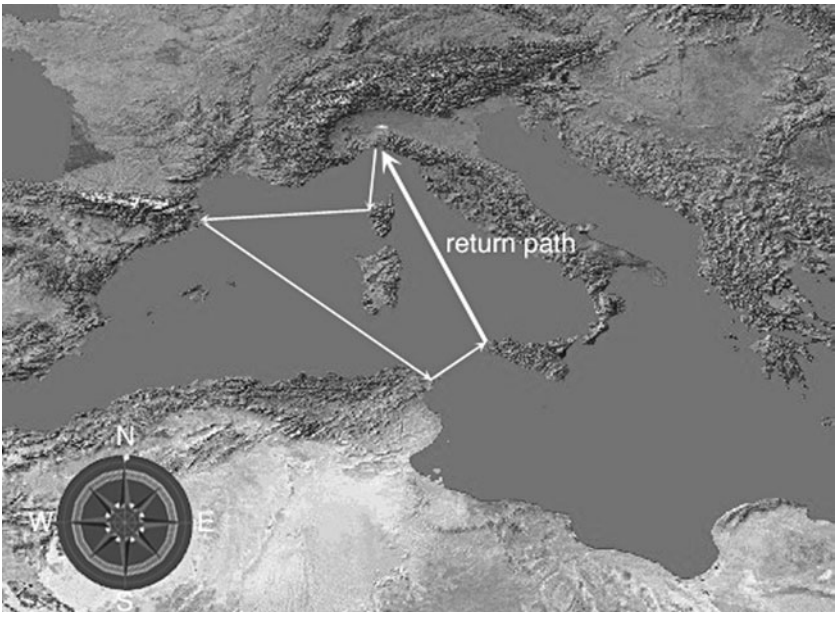

Figure 11.7. Dead-reckoning navigation (path integration). Keeping track of distances and directions at each segment of the travel, one can calculate the shortest return path to home base.

was not particularly reliable in the vast waters of the Atlantic Ocean. A new method, celestial navigation, was adopted. Celestial navigation determines one's geographic position by means of astronomical observations (distal cues). For example, one can use the sun during the day and Polaris (the North Star), a star near the North Celestial Pole known to every sailor, by night. It is fairly easy to roughly estimate latitude by looking at the sun or Polaris. Each star has a celestial latitude, or declination. Even if a star is not directly overhead, by calculating the angle between the star and the overhead point (called the zenith), the latitude can be deduced.[38]

In its simplest form, celestial or landmark navigation is a *triangulation* problem. Triangulation involves affixing an object's location via triangles. One can estimate position and travel distance by keeping track of the angles between the navigator and a distant landmark. If at least two fixed landmarks are available, positioning becomes a simple trigonometric problem, in which process time is irrelevant. But one has to be able to see or otherwise sense the landmarks. On land, a

38. Because heavenly bodies are not stationary, the measurement must be made at the time of night when the star in question is highest in the sky. Columbus learned about celestial navigation from the Portuguese sailors and attempted to use it. However, his logs reveal how poorly he calculated geographical position, even by the standards of his day (Pickering, 1996).

detailed map can be created through tessellation, which exploits the principle from floor tiling that every part of a surface can be covered by polygons of the same size and shape without any gaps or overlaps.[39] These polygons can then provide fixed reference points.

Celestial or landmark navigation is a superior form of navigation, but it needs a map, which first must be created by prior dead-reckoning navigation. In the absence of visible landmarks or astronomical anchor points, the navigator can only rely on dead reckoning. In addition to humans, all mammals and even lower forms of animals seem to flexibly use both dead-reckoning and triangulation methods of navigation.[40] Humans invented principles for navigation that have been in use by other animals for millions of years. But what do navigation methods have to do with brain oscillations and memory? You will soon see the relevance of my story about nautical explorers.

Place Cells and Maps in the Hippocampus and Entorhinal Cortex

Finding behavioral correlates of single neurons in central structures such as the hippocampus is a daunting task because this central structure is so far removed from the peripheral inputs. Nevertheless, when a hippocampal pyramidal cell fires while the rat is freely navigating in its home cage or the testing apparatus, it is enough to watch the animal and listen to the loudspeaker broadcasting the cell's spikes to recognize that the neuron's activity is distinctly related to the rat's visits to a circumscribed small location. It is a memorable experience for anyone listening to a well-tuned "place cell," a term referring to the receptive or decoding features of pyramidal and granule cells. This striking relationship in only eight of the several dozens of the recorded neurons was enough for John O'Keefe at University College London to declare in 1971 that hippocampal neurons code for the Cartesian position of the rat, irrespective of its behavior and regardless of the direction from which it came to its position.[41] This observation was a major breakthrough because it showed a clear relationship between an overt behavior and single units in a high-level associative structure.[42] In his follow-up studies, O'Keefe

39. Tessellation (from Latin *tessera* for square tablet) of a plane using identical shapes is possible with either equilateral triangles or quadrilaterals. An important idea that can be illustrated through tessellations is symmetry. Plane symmetry involves moving all points around the plane so that their positions relative to each other remain the same.

40. Rommell and McCleave (1972), Walcott and Green (1974), Baker (1980), Mittelstaedt and Mittelstaedt (1980), and Redish (1999).

41. O'Keefe and Dostrovsky (1971). It is not clear how many of the eight cells in this original landmark study were true place cells because they fired when the "rat was facing in a particular direction," a criterion for head-direction cells rather than omnidirectional place cells.

42. Several studies prior to O'Keefe's seminal discovery examined the behavioral correlates of hippocampal unit activity. Ranck (1973) listed more than 20 behavioral correlates of unit activity. The

demonstrated that every hippocampal pyramidal neuron has a place correlate, and by inference, every part of space is represented by the discharge of some hippocampal neurons. O'Keefe teamed up with another protégé of Donald Hebb, Lynn Nadel, and they expanded their observations into a large-scale theory. The book that contains these ideas has remained the opus magnum of all prior works written about the hippocampus.[43] In essence, the authors argued that the hippocampus computes the allocentric ("other–than–self-centered") space, similar to landmark or celestial navigation of Portuguese mariners. Information from all modalities enters the hippocampal networks by way of the entorhinal cortex and a map comes out; it is a conceived or holistic cognitive map, which allows the animal to navigate much the same way as we do when in possession of a map. We can make shortcuts, solve detour problems, and plan a trip economically to several cities on a single trip.

Over the past 30 years, O'Keefe and other investigators have discovered numerous important features of place cells. In a two-dimensional environment, which is the normal ecological space for most rat strains in the wild, the place fields are cone shaped, with the center determined by the highest firing rate of the neuron (figure 11.8); that is, the firing rate increases identically, independent of the direction from which the rat arrives. This *omnidirectional* property indicates that place neurons are not coding for simple sensory stimuli but instead are computing an *explicit location* of the environment. Removal of a variety of cues in the environment does not affect the firing pattern as long as a few cues remain available. On the other hand, when the distant room cues are rotated together or the animal's testing box is moved to another room, place cells will rotate with the cues or "remap," supporting the idea that it is the distant landmarks that guide map construction.[44] As long as the landmarks stay put, place cells are stable in the same environment for months. Only a small fraction of all pyramidal cells fire in any given environment, and those that do remain pretty much silent outside their field. This sparsity feature, together with their hypothesized explicit spatial computation, qualifies place cells as gnostic units.[45]

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lasting contribution of his monograph is the recognition of two types of hippocampal CA1 neurons: complex spikes cells and theta cells, which later were identified as pyramidal cells and a subset of fast-firing interneurons phase-locked to the theta waves. Other early single-unit studies include Noda et al. (1969), Thompson (1976), and works from James Olds's laboratory (e.g., Segal et al., 1972) and Vinogradova's laboratory (summarized in Vinogradova (2001).

43. O'Keefe and Nadel (1978). The manuscript was circulated among their peers for almost 5 years before it was submitted for publication. Neither author had more than a handful of published papers prior to their book. In the absence of MedLine and the Internet, the book also became a referenced encyclopedia of hippocampus research. There are numerous tables in the book that list the observations and interpretations of other investigators, citing virtually every relevant experiment performed on the topic in the Western hemisphere.

44. These features should remind us that re-creation or completion of the whole from fragmentary inputs is the hallmark of autoassociative networks (Wills et al., 2005).

45. In humans, this explicitness is illustrated by the observations that some hippocampal units respond invariantly to the different views of the same person or object independent of size or background or whether it is a photograph, a cartoon, or a written name (Heit et al., 1998; Quiroga et al., 2005). Explicit (semantic) representation implies high logical depth and invariance to nonspecific

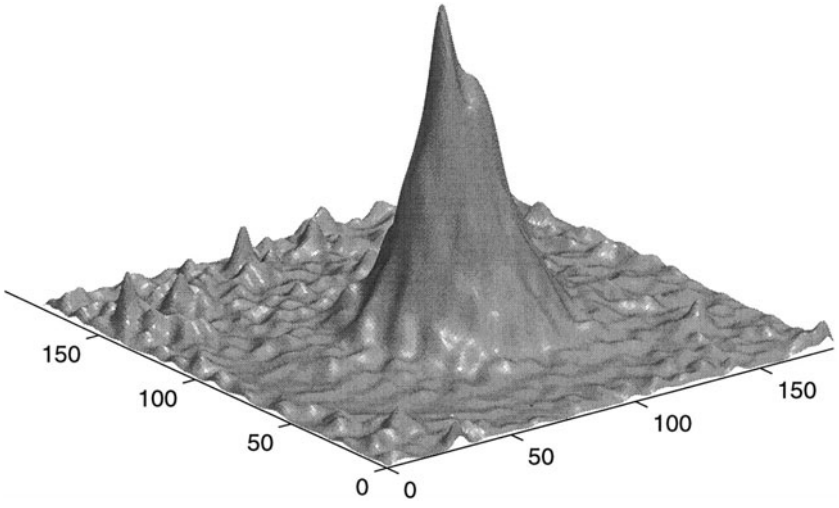

Figure 11.8. Explicit representation by a CA1 place cell of the animal's position in a two-dimensional environment. Distances are in centimeters on the x- and z-axes. The y-axis (vertical) is the firing rate of the neuron. Note the cone shape (omnidirectionality) of the place field with a 40- to 50-centimenter base. The shape of the place field does not depend on velocity, acceleration, or past or future trajectory of motion of the rat, but the height of the field (i.e., frequency of discharge) does. Reprinted, with permission, from Samsonovich and McNaughton (1997).

Recent studies by Edvard and May-Britt Moser and colleagues at the Center for the Biology of Memory in Trondheim, Norway, identified the immediate origin of the allocentric map in the layer 2 cell population of the dorsomedial entorhinal cortex. These neurons are the major recipients of the information from the visual and parietal cortices and give rise to the major input to the hippocampal granule cells and CA3 pyramidal neurons. However, unlike hippocampal place cells, which have an explicit, single receptive field, the entorhinal neurons are activated whenever the animal's position coincides with any vertex of a grid of equilateral triangles spanning the entire surface of the environment. Hence their name: "grid cells" (figure 11.9). The grid size is approximately 30 centimeters, echoing the size of a typical hippocampal place field, and neighboring entorhinal neurons display the rotated or displaced versions of the same tessellating structure.[46] The periodically organized entorhinal map is a rigid map because coactive

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information (Von Neuman, 1956). Logical depth refers to the number of computational steps required to reach a conclusion (Koch 2004). Semantic items typically require only one step, whereas items in an episode require several steps of computation.

46. Grid size of neurons increases from the dorsal to the ventral part of the medial entorhinal cortex, a pattern that is also reflected by the increasing size of place fields in the septotemporal axis of the hippocampus (Jung et al., 1994). Thus, the spatial distances are represented by multiple scales in both the entorhinal cortex and hippocampus.

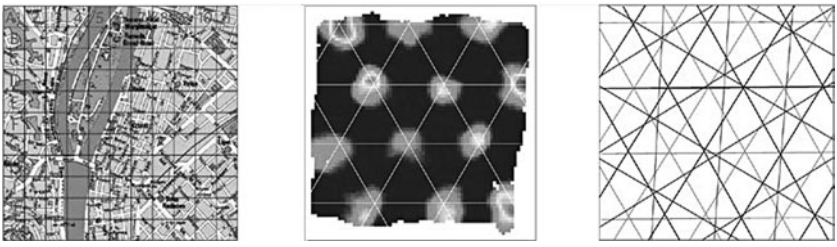

Figure 11.9. Gridlike representation of the environment by entorhinal place cells. Left: Tessellation of a city map by squares provides information about position, distance, and direction, allowing specific places to be easily located. Middle: As a rat explores an experimental enclosure (1 m^2), the discharge rate of a neuron in the dorsocaudal medial entorhinal cortex increases at regular intervals corresponding to the vertices of a triangular grid (Figure courtesy of Edvard Moser). Each of the 12 place fields of the single neuron is similar to the cone shape shown in figure 11.8. Right: Integration of information from several grid components (i.e., from the outputs of several neurons) can increase the spatial resolution of the environment. Reprinted, with permission, from Buzsáki (2005a).

grid cells remain in register when the rat is moved to another apparatus with a different size or shape or is tested in the same apparatus but in a different room.[47] In contrast, hippocampal maps are flexible, and unique cell assemblies are called upon in different environments. Importantly, grid cells become active instantaneously in any novel environment, whereas establishment of stable place cells in the hippocampus may take from minutes to days of learning.[48] Thus, there are similarities as well as important differences between hippocampal and entorhinal cortical representation of the environment.

A map is the embodiment of the spatial relations among landmarks. It allows for the computation of position, distance, and direction and assists effective navigation. How can one identify maps of the environment in the brain? In contrast to the orderly and constant relationship of objects in the environment, a consistent finding is that physically nearby neurons in the hippocampus do not code for neighboring places (figure 11.10).[49] The random graph architecture of the hippocampus does not reveal a simple physiological topology. The brain structure that gives rise to explicit maps does not have a strict topographic organization. It

47. Although the grid structure remains unaltered in two different environments, the grids may shift in a particular direction (E. Moser, personal communication).

48. In contrast to the plane symmetry features of entorhinal cells (Hafting et al., 2005), the context-dependent remapping of hippocampal neurons is the telltale sign of symmetry braking. Lever et al. (2002) observed that when rats are repeatedly exposed to two differently shaped environments, hippocampal place-cell fields in the respective environments diverged over several days. Their findings indicate that place cells may be a neural substrate for long-term incidental learning. This flexibility of context is in contrast to the original formulation of hippocampal place cells (O'Keefe and Nadel, 1978), which stated, following Kant, that representation of the environment is innate.

49. For a quantitative analysis of the relationship between spatial locations and physical locations of place cells in the hippocampus, see Redish et al. (2001).

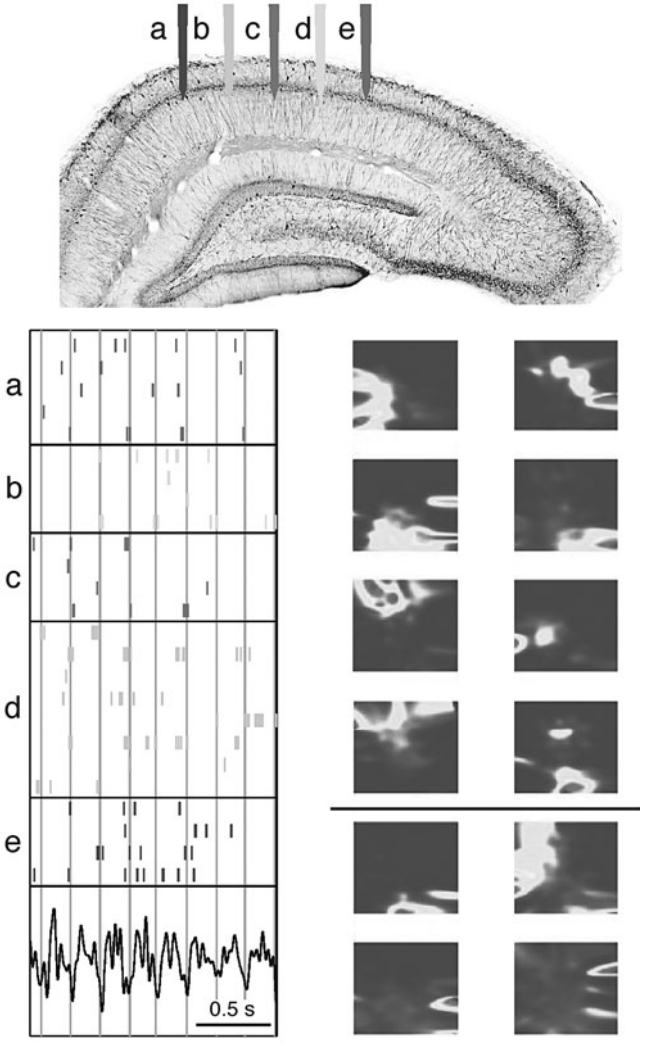

Figure 11.10. Absence of topographical representation of the environment in the hippocampus: five recording electrodes placed in the CA1 pyramidal layer (top) and corresponding unit discharges over a short period (left). Right: Place fields of neurons from two electrodes (separated by the horizontal line). Note the random representation of place segments in the apparatus with a square-shape floor, viewed from above, by neighboring neurons. Light areas represent neuronal discharges of individual hippocampal neurons.

does not have to. Orderly maps can be constructed by random connections, as well, although reading the routes may first appear complicated. Suppose that we would like to drive from New York to San Francisco. By consulting the road map of the United States, we can calculate the shortest path by measuring the distances of the roads connecting the different cities along the way. If we make a paper ball

out of the map, the route information remains preserved, but finding the shortest path now gets a bit trickier.[50]

In the hippocampus, the two major elements of the route-finding optimization procedure are the omnidirectional, explicit place cells and the synaptic strengths between them. An appropriate algorithm can easily calculate the shortest, that is, the most effective, route between any two neurons (figure 11.5). Thus, searching for a path in neuronal space is analogous to reading a map. The essential isomorphism between the strongly recurrent CA3 network and two-dimensional Cartesian space was first conceived by Robert Muller at the Downstate Medical Center in Brooklyn and the graph theorist János Pach at the Courant Institute in New York. They hypothesized that every path in Cartesian space can be described as a path in neuronal space (neuron–synapse–neuron route).[51] The key intuition here is that the distance between positions represented by two place cells is coded by synaptic strength between the neurons. Neurons representing nearby locations are connected by stronger synapses than are neurons representing more distant locations. In a randomly connected neuronal graph, maps can therefore be stored even if the physical locations of place cells in the hippocampus and entorhinal cortex have no resemblance to the layout of the environment they represent. Although not much experimental support was available to back up their hypothesis, the modeling results of Muller and Pach showed that the best paths in two-dimensional space associated with best paths in neuronal space approached straight line segments (i.e., shortest possible path lengths) as the divergence of single neurons in the model system increased. In essence, the neuron graph model demonstrated the conceptually similar nature of finding the shortest routes in real and neuronal space. Graph-searching algorithms in the neuronal-synaptic space effectively calculated shortcuts when road blocks were removed or the shortest route when faced with a detour problem.[52]

The omnidirectional features of place cells and the equipotential tessellation features of entorhinal cortical cells illustrate the important concept of plane

50. Another, more persuasive explanation for the lack of a physical resemblance between the environment and the functional connections is that the hippocampus stores many maps, one for each environment (Muller et al., 1996b; Samsonovich and McNaughton 1997).

51. (Muller et al., 1996b). Maps can be constructed by various neuronal architectures, because maplike representation are present in most animals from insects to mammals with different types of brains (Gallistel, 1990). However, the CA3 autoassociator can allow for the flexible use of multiple independent maps, unlike the rigid single map representation of grid cells in the dorsomedial entorhinal cortex (Hafting et al., 2005). Furthermore, the synaptic-weight–guided connections are exactly the sort of architecture needed for attractor dynamics. Samsonovich and McNaughton (1997), building on the graph representation of the environment, demonstrated how multiple graphs or charts can coexist in a hippocampal model to flexibly represent multiple environs.

52. The synaptic graph model, in its originally conceived version, is not feasible physiologically, however. Synapses between pyramidal cells are weak, and the activity cannot spread from one neuron to another. Nevertheless, the conceptual simplification of Muller et al. (1996b) has far-reaching consequences for understanding the utility of a high-dimensional autoassociator for coding and retrieving information. Once single cells are substituted with cell assemblies, the effectiveness of assembly communication can be assessed by large-scale recordings of neurons even without measuring the synaptic weights directly between neuron pairs.

symmetry. Plane symmetry involves moving all points around the plane so that their positions relative to each other remain the same. Symmetries preserve distances, angles, sizes, and shapes. The plane symmetry representation by explicit place cells in the entorhinal grid cells is in stark contrast to the asymmetric recall features of episodic memory. Episodic recall moves forward in time, whereas maps do not require time dimension. Yet, I suggested above that the strongly connected, directed, and weighted graph of the CA3 autoassociator and the CA3–CA1 synaptic matrix is an ideal architecture for storing and recalling episodic information. The conflict is even more apparent at the conceptual level, because map-based navigation is an allocentric concept, whereas the essence of episodic memories is egocentric, self-referenced, first-person representation.[53] To solve the conflict between spatial mapping and episodic memory, we need to add two more ingredients to hippocampal neuronal patterns: symmetry braking of routes and temporal context. A useful step in this direction is to examine how maps are constructed and calibrated in the first place.

Dead Reckoning by the Hippocampus: Maps Are Made through Motor Actions

Imagine that you are transported to a dark room while asleep, and you wake up in that totally unknown environment. Walking in random directions, you may come to a wall. Remembering the number of steps it took you to reach the wall and the direction of motion, you can easily return to the start position. Continued walking in the opposite direction will take you to the opposite wall. From the total number of steps, you have a sense of the distance between the two walls. Using the same dead-reckoning strategy, the distances between all walls and all possible objects identified in the room can be estimated. After sufficient amount of exploration, that is, dead-reckoning navigation, you can form an internal image, often referred to as a mental or cognitive map, of the room that allows you to make shortcut and detours. The method of map formation is fundamentally the same in the light. Although you can often estimate distances on the basis of visual cues, as well, making map formation faster than in the dark, such visual distance estimation by eye movements is based on previous locomotor practice. We are not born with these metrics in our heads. They are developed through active locomotion. Map-based navigation requires a calibrated representation of the environment. The dictum "no action—no perception" (Cycle 8) also applies to the navigation system.[54]

53. Ego/allo, self/other distinctions have resurfaced several times in the history of neuroscience. Hughling Jackson used the term "subject consciousness" for our first, personalized awareness of our subjective self and distinguished it from "object consciousness," which refers to the other things "out there" in the environment.

54. Whishaw and Brooks (1999) trained rats to forage on an open table for a large food pellet, which the rats could carry back to a refuge. In the test phase of the experiment, the location of the refuge from which the rats emerged was changed. In these trials, all rats first explored the table with

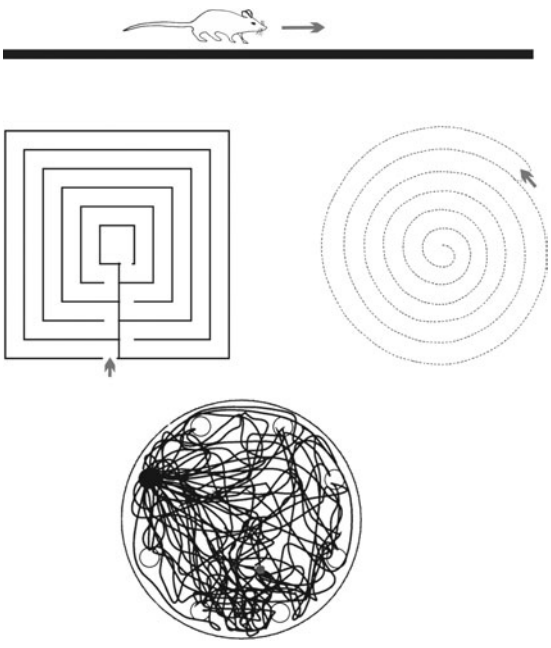

Figure 11.11. Generation of a map requires exploration with path crossings (junctions). Dead-reckoning navigation on a linear track, complex maze, or spiral maze without path crossings and distant landmarks cannot establish anchor points and maps. Travel is based exclusively on self-referenced cues. Exploration in an open environment, on the other hand, such as a large cylinder, is random walk navigation, during which paths are recrossed multiple times. Such multiple path junctions are hypothesized to generate omnidirectional hippocampal place cells. Reprinted, with permission, from Buzsáki (2005b).

However, movement itself is not sufficient to develop a map. If in our dark room example you walk in a spiral without crossing paths and reexperiencing the same objects (landmarks) from different directions, a map does not develop. The same is true for any one-dimensional travel, for example, moving back and forth on a straight line or running on a treadmill. However, dead-reckoning exploration is essentially a random-walk type of navigation during which the paths of navigation often cross (figure 11.11).[55] As a result, the intersections will be tied to multiple routes. The landmark junctions are critical for correcting the positional

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the same vigor under both light and dark conditions before navigating home in a straight line with the food, even though the available landmarks, in principle, provided the appropriate direction and distance to find the reward and return to the refuge.

55. The random-walk analogy is not true for the whole extent of behavior. Rodents adopt specific locations in their home environment, and even featureless environments, as home bases from which they organize exploratory trips. The excursions from the home bases are circuitous and consist of a number of progressions punctuated by stops. Typically, excursions are terminated by fast, direct returns to the home base. These behavioral patterns are altered after hippocampal damage (Whishaw et al., 2001).

errors and for the construction of a map. Once in possession of a map, landmark navigation is a superior form of navigation and is likely chosen by all animals that can generate such representation. In the absence of landmarks, on the other hand, animals can always rely on dead reckoning. It follows that dead-reckoning and map-based navigations are interchangeable only *after* a map has been established as a result of dead-reckoning exploration, because two-dimensional maps *evolve* from junction crossings of one-dimensional routes.

An important justification for distinguishing between one- and two-dimensional travels is that such a distinction appears important to the brain. When a rat runs back and forth in a straight alley, different sets of hippocampal neurons are active on the opposite journeys.[56] The direction-dependent or *unidirectional* firing of neurons in a one-dimensional task is in sharp contrast to the plane-symmetric, omnidirectional discharge of place cells in two-dimensional environments. This observation also indicates that the firing rate of single cells alone is not a foolproof correlate of the animal's momentary position. Although environmental cues may exert effective control on the firing rate of hippocampal cells, other types of inputs are also important. One such strong influence is the speed at which the animal moves through the place field. Speed information may come from multiple sources, including the vestibular system, optical flow, and reafferent signals from the muscles and muscle tendons. András Czurkó and Hajime Hirase, working in my laboratory, have identified reafferentation as a critical source of speed information. Recording from place cells while the rat was running in a wheel, we found a linear relationship between firing discharge of the neurons and running velocity (figure 11.12). Optical flow and vestibular input appeared to be of secondary importance because the head was quite stationary in the wheel and the velocity-firing rate relationship remained the same in complete darkness. Importantly, scalar speed did not modulate the firing rate of just any cell but increased the rate only when the rat's head was within the boundaries of its place field. In fact, increasing speed may decrease the rate when the rat runs in a direction opposite to the favored direction of the cell.[57]

These findings in the wheel experiment not only demonstrate direction-specific firing in another one-dimensional task but also show that the firing rate of single cells is a combination of both location and the velocity of the animal.[58] The engineering notion of such combinatorial property is "gain."[59] Velocity is a gain factor

56. McNaughton et al. (1983a) found that in an eight-arm radial maze, place cells often fire only in one direction of motion, some during the outbound, and others during the inbound journeys but not both directions. This was also the first report to note the effect of locomotor velocity on the discharge rate of hippocampal place cells.

57. The direction-specific firing of hippocampal neurons in the wheel with the rat's head kept relatively stationary is reminiscent of "view cells" in head-fixed monkeys (Rolls 1999).

58. Neurons in the wheel have unidirectional place fields (Czurkó et al., 1999; Hirase et al., 1999). For the conditional signal enhancement of place-cell activity, see Moita et al. (2003).

59. The different inputs are not simply summated, and the idea of "gain" is different from "conjunctive" neurons, which refer to a new quality that arises from a combination of singular features (e.g., Deadwyler and Hampson, 1997; Eichenbaum, 2002). E.g., the environmental context can select the neuronal assembly, whereas gain control (provided by local cues, locomotion speed, emotional state, and other factors) can differentially adjust the firing rate of the assembly members (Leutgeb et al., 2005).

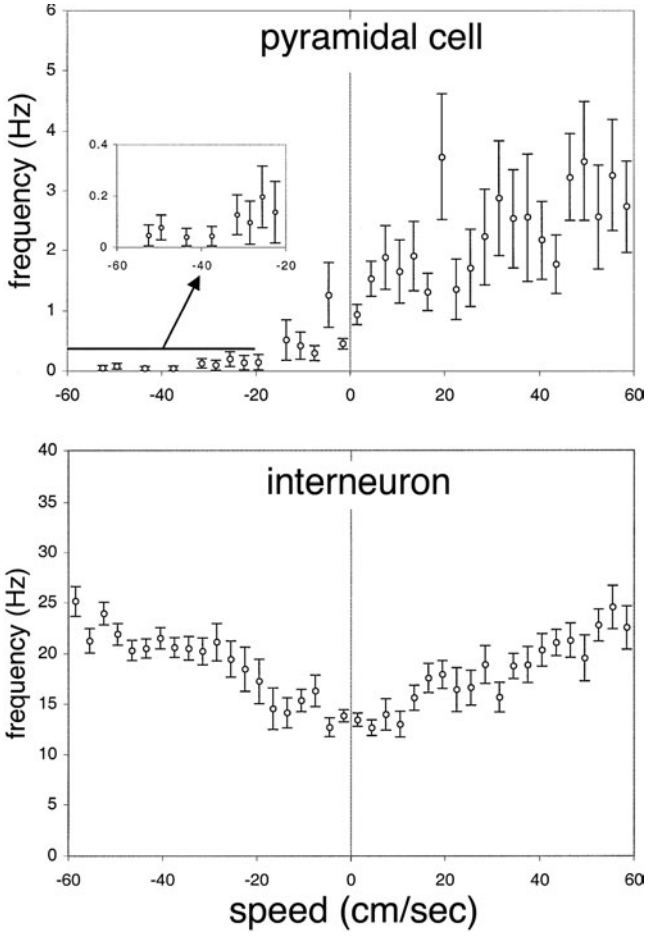

Figure 11.12. Gain modulation of neuronal activity. Top: Firing rate of a pyramidal cell as a function of running speed. The rat was running in a wheel so that the spatial and body-reference signals were kept constant. Negative and positive speed values indicate running directions to the left and right, respectively. Note suppression of discharge rate in the non-preferred direction. Bottom: Interneurons show only a moderate speed dependence, and independent of the direction of running. Reprinted, with permission, from Czurkó et al. (1999).

that enhances the sensitivity of hippocampal place cells to provide a greater output.[60] Because of gain control, the discharge rate of single cells is always ambiguous for defining location. For now, however, the important thing to remember is that speed information is available in the hippocampal system. To derive velocity

60. Similar "gain control" has been described in other systems, as well. In the posterior parietal cortex, a neuron's firing response is expressed as the product of the visual response relative to the retina (the cell's conventionally defined receptive field) and the position of the eye within its orbit

(i.e., a vector) from speed, direction is needed, as well. The source of this critical information was revealed by James Ranck from State University of New York–Brooklyn at a small meeting of hippocampus aficionados in 1984. "Head-direction" neurons in the postsubiculum, part of the subicular complex between the hippocampus and entorhinal cortex, fire only when the head points in a certain direction in the environment, regardless of the neck angle or the animal's location.[61] A set of head-direction cells can function as a compass, a handy instrument in dead-reckoning navigation. However, the target of head-direction cells is not Earth's magnetic field but some arbitrary reference direction, which may shift when cues in the laboratory are rotated in a coherent manner. There are many sets of head-direction cells tuned to different arbitrary directions. Ranck's student Jeffrey Taube, now at Dartmouth College, and Alain Berthoz's group at College de France in Paris have searched for head-direction cells outside the postsubiculum and identified a whole system of head-direction cells in the brain. Varying fractions of neurons in the anterior thalamic nuclei, lateral dorsal thalamus, posterior parietal and retrosplenial cortices, dorsal striatum, lateral septum, dorsal tegmental nucleus, lateral mammillary nucleus, and entorhinal cortex show head-direction properties. Importantly, the direction system can function independent of the hippocampal place cells, because damage or inactivation of the hippocampus does not abolish directional tuning of head-direction cells.[62] In addition to direction, many cells in the lateral mammillary body also respond to the angular velocity of the head. So there is a common thread here with position-reporting place cells: both navigational systems are gain-modulated by speed signals. The properties described above endow the system of head-direction neurons with the ability to signal the rat's sense of direction during navigation.

These and related findings appeared sufficiently strong exceptions to the omnidirectional place-cell–based landmark navigation to Bruce McNaughton at University of Arizona–Tucson that he challenged the map theory of the hippocampus.[63] In a conceptually similar set of experiments, McNaughton and O'Keefe examined the critical determinants of place cells. In the London experiment, the rats were tested in rectangular boxes of various sizes and shapes. Place fields recorded in a small square box became elongated or even split into two place fields when the rat was put

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(Andersen et al., 1997; Zipser and Andersen, 1988). In visual area V4, saccadic eye movements enhance the firing rates of only those neurons that are driven by their preferred inputs (Sharma et al., 2003; Bichot et al., 2005).

61. Ranck (1985).

62. For comprehensive reviews on the head-direction system, see Taube and Bassett (2003) and Muller et al. (1996a). Firing of thalamic head-direction cells is also correlated with the speed of head turning (Blair and Sharp, 1995). Some neurons in the subicular complex show both spatial and directional properties (Sharp and Green, 1994; Cacucci et al., 2004). Head-direction cells allow the reorientation in a familiar environment as rapidly as 80 milliseconds after changes in the visual scene (Zugaro et al., 2003), i.e., about one theta cycle.

63. The main arguments in favor of the hippocampus-based dead-reckoning navigation are summarized in a landmark paper (McNaughton et al., 1996). A formal model of path integration is presented in Samsonovich and McNaughton (1997). At about the same time, Touretzky and Redish (1996) also developed a computational model of dead reckoning (see also Redish, 1999).

in a double-size rectangular test box. Often, the newly created split place fields became directional, with the preferred directions of each half oriented toward each other. The rats in the Tucson experiment had to shuffle back and forth between two food sites on a linear track. In some trials, the distance between the two sites was reduced. As a result, the size of the place fields became compressed and occasionally disappeared altogether. O'Keefe and his long-term collaborator Neil Burgess provided a geometrical explanation, suggesting that the rat calculated the box sizes by triangulation on the basis of vertical heights of the walls and other visual cues. McNaughton offered an alternative explanation: dead reckoning or path integration.[64] One of his key arguments is that seeing or otherwise sensing distant landmarks is not sufficient to activate place cells. Instead, distance is calculated on the basis of self-motion cues. During locomotion, the rat remembers each physical contact with the wall and monitors the amount and direction of movement from the contacted landmark for the computation of vectorial distance. In an enviably simple experiment, his group has already shown that it is sufficient to wrap the rat tightly in a towel: under such conditions of movement restraint, both place cells and thalamic head-direction cells become virtually silent, even when the animal is moved through the place fields by the experimenter. In another experiment, the rat either actively ran around a circular track or "drove" a toy car, or the curtain surrounding the track was rotated while the rat was sitting. The firing rate of the place cells was proportional to the movement generated by the rat and to the power of theta oscillation.[65]

The main ingredients of McNaughton's dead-reckoning model are the multimodal sensory inputs, direction of self-motion, hippocampal place cells, and a hypothetical integrator. Direction is calculated by the head-direction system residing outside the hippocampus. This information feeds the hippocampal place-cell system, which functions as a two-dimensional attractor that calculates the shortest distances between landmarks with the help of the integrator. The integrator receives inputs from all other components of the path integrator machinery and calculates all possible combinations of head orientation and location.[66]

64. O'Keefe and Burgess (1996) and Gothard et al. (1996). The term "path integration" was adopted from Mittelstaedt and Mittelstaedt (1980), who showed a gerbil mother, after searching for a missing pup in the dark by an apparent random walk, returned to the nest in a straight line after the pup was found. Path integration and dead reckoning are synonymous terms.

65. Foster et al. (1989) showed the silencing effect of immobilization on place cells, and Knierim et al. (1995), on head-direction neurons. The active and "toy car driving" experiments are reported in Terrazas et al. (2005).

66. The location of the integrator in the Samsonovich and McNaughton (1997) model was tentatively identified with the subicular complex. Another option for integration is the entorhinal cortex. Egorov et al. (2002) reported that transient depolarization of layer 5 neurons causes a persistent firing, with discharge rates commensurate with the magnitude of depolarization. Conversely, transient hyperpolarization reduces firing rate in a steplike manner. The tessellation feature of entorhinal cortical neurons is also consistent with the notion that integration of position, direction, and distance may take place in the entorhinal cortex (Hafting et al., 2005). Indeed, head-direction cells are also present in the dorsomedial entorhinal cortex. Layer 5 neurons are explicit head-direction cells, whereas layer 3 neurons show both grid tessellation and head-direction properties (K. Mizuseki and G. Buzsáki, unpublished observations; E. Moser, personal communication). Thus, place and direction information are present in single entorhinal cortical modules.

The idea that the hippocampus contributes to dead reckoning indirectly brought time back into the picture, the fundamental dimension for episodic memory. Thus, this is the point at which, without the discussion of a timing mechanism, I cannot develop the discussion further. Furthermore, we still have to understand how distances are converted into synaptic weights in the autoassociative attractor networks of the hippocampus and in the grid map of the entorhinal cortex. Because both dead reckoning and episodic memory depend on time, and because both processes are self-centered, there may be a link between them. Furthermore, the relationship with allocentric maps and semantic (allocentric explicit) memory, also attributed to the activity of the hippocampal–entorhinal system, remains to be elucidated, as well.[67] Before we can move on with these difficult issues, I provide an overview of the theta rhythm, the major temporal organizer of the hippocampal–entorhinal cortex. My main claim is that it is the theta oscillation through which one can understand the relationship between one-dimensional and two-dimensional navigation and between episodic and semantic memory.

Theta: The Rhythm of Navigation in Physical and Neuronal Space

Hippocampal theta oscillations (6–10 hertz in the rat and somewhat slower in higher species) are different from all cortical rhythms discussed so far. Theta oscillation is a sustained rhythm in the sense that as long as the animal is engaged in the same behavior, theta waves occur continuously.[68] As alluded to in Cycle 1, the exact behavioral categories associated with theta have never been agreed upon. I have used the term "exploration" in my writings to avoid the connotation of "voluntary" or "attentional" behavior, but it is arguable whether walking the same alley for the hundredth time is still considered exploration. Navigation is perhaps the best descriptive term, implying both self-motion and mnemonic navigation in neuronal space.[69]

Generation of Theta Rhythms

Neurons in many structures, including all those illustrated in figure 11.3, can fire phase-locked to hippocampal theta oscillations, although the extent of the phase

67. The discovery of neurons predicting the future choice of the animal in a T-maze task also provides support for the hypothesized link between dead reckoning and episodic memory (Frank et al., 2000; Wood et al., 2000; Ferbinteanu and Shapiro, 2003).

68. More than 1,600 reports have been published on theta oscillations over the past six decades. I can only briefly highlight the major milestones here. I refer the reader to the several comprehensive reviews on the topic (Grastyán et al., 1959; Buzsáki et al., 1983, 1994a; O'Keefe and Nadel, 1978; Bland, 1986; Vanderwolf, 1988, 2003; Lopes da Silva et al., 1990; Stewart and Fox, 1990; Vinogradova, 1995, 2001; Vertes and Kocsis, 1997; Buzsáki, 2002, 2005b). For theta oscillation's role in plasticity, see Larson and Lynch G (1986) and Huerta and Lisman (1993; 1995).

69. Theta oscillation is also the hallmark of REM sleep (Jouvet, 1999, 2004; Grastyán and Karmos,1961)).

entrainment depends on structure, cell type, and task. In such a strongly interconnected system with multiple loops, identifying the key ingredients responsible for the emergence of the rhythm is not trivial. The simplest and oldest idea is that a "pacemaker" is responsible for it all. Helmut Petsche at the Brain Research Institute in Vienna pointed to the cholinergic medial septum as the theta pacemaker more than four decades ago. Recently, the supramammillary nucleus, a structure in the hypothalamus with bidirectional connections with the septum, emerged as a supplementary pacemaker candidate.[70] Petsche and many subsequent investigators have shown that complete destruction of the medial septum abolished theta in the hippocampus and, by implication, in all related structures. This could be because the septum, as postulated, is an independent pacemaker or rhythm generator. Alternatively, its connections may lie at a critical crossroad of the loop(s) of structures that collectively give rise to the rhythm.

In support of the pacemaker idea, septal and other basal forebrain cells that release the neurotransmitter acetylcholine or GABA can sustain bursts of action potentials at theta frequency. In other words, they are endowed with the proper time constant and necessary intrinsic mechanisms to sustain subthreshold and suprathreshold oscillations. What has never been shown, however, is whether the circuitry that entrains these individual neurons into a synchronous action resides in the septum itself, assisted, for example, by its own GABAergic neurons, or requires feedback from other structures, such as the hippocampus. The role of the neurotransmitter acetylcholine is rather complex. For example, pharmacological blockade of the action of acetylcholine does not significantly affect locomotion-related theta, although the drug effect can be revealed by the reduction or abolishment of theta waves induced by meaningful sensory inputs in the absence of movement. On the other hand, selective and complete damage to the cholinergic cells in the septal area decreases the amplitude of hippocampal theta oscillations several-fold, although it does not completely eliminate it. In contrast, application of cholinergic drugs can induce transient thetalike oscillations in hippocampal slices, that is, without the septum.[71] This "*in vitro* theta" depends on the excitatory recurrent collaterals of the CA3 autoassociator as well as on hitherto not well-understood interactions with interneurons. With Anatol Bragin in my lab and Bernard Kocsis at Harvard University, we have shown that the CA3 theta generator functions relatively independently of other theta generators in the intact brain. Thus, at least one theta oscillator that is supported by the hippocampal networks requires a permissive action of the medial septal cholinergic input but no external timing.

GABAergic hippocampal interneurons have also been implied in theta oscillations ever since Ranck's finding of rhythmic "theta" cells in the navigating rat.[72]

70. Petsche et al. (1962).

71. Bland et al. (1988) introduced the slice preparation for the study of *in vitro* rhythms. For reviews of thetalike and gammalike oscillations *in vitro,* see Traub et al. (1999, 2004).

72. The interneuron identity of "theta cells" (Ranck, 1973) was a controversial issue for a long time. Brian Bland and his post-doctoral advisor Per Andersen, the authority on both *in vivo* and *in vitro* cellular physiology, concluded that the granule cells in the anesthetized rabbit are the most rhythmic and best locked to the phase of theta oscillation in the hippocampus, followed by pyramidal cells,

Tamàs Freund's group at the Institute of Experimental Mecicine, Budapest, Hungary has been at the forefront of working out the relevant microcircuitry in the septohippocampal GABAergic system. Their most remarkable discovery is the selective nature of connections within the GABAergic population. GABAergic cells in the medial septum project to all types of hippocampal interneurons but do not contact pyramidal cells or granule cells at all. In turn, long-range interneurons are the only hippocampal cells that project back to the medial septum, innervating the cells of origin, and may be responsible for synchronizing the neuron populations in the medial septal nucleus. A case similar to the postulated medial septal pacemaker can be made also for a special group of interneurons, the oriens–lacunosum-moleculare (O-LM) cells. The dendrites of O-LM neurons are confined to the oriens layer and are innervated mainly by CA1 pyramidal cells; their axons innervate mostly the distal apical dendrites of the pyramidal cells. Like the cholinergic septal cells, O-LM interneurons are endowed with the necessary intrinsic properties to oscillate at theta frequency individually. Their propensity to oscillate is made possible mainly by the especially high density of channels responsible for the pacemaker current I_h. However, for a coordinated group action, the O-LM neurons have to be synchronized, a job that can be accomplished by either the faster firing basket cells or the long-range neurons (figure 11.13).[73]

There are other critical ingredients to add. Although hippocampal pyramidal cells do not typically oscillate in isolation, they have resonant properties at theta frequency, due mainly to the time constants of currents flowing through ion channels known as I_h and I_m .[74] Layer 2 entorhinal cortical neurons (the grid cells), on the other hand, are endowed with subthreshold oscillations at theta frequency. The oscillation is a result of the dynamic interplay between two opposing forces, a depolarization-activated persistent inward current (so-called I_{NaP}) and the hyperpolarization-activated pacemaker current (I_h).

My goal with this short survey was to demonstrate that evolution has dedicated a consortium of mechanisms to secure a precise timing mechanism at the theta

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whereas GABAergic interneurons hardly ever fire rhythmically or phase-locked to theta (Bland et al., 1980). Our *in vivo* intracellular labeling studies provided the conclusive evidence that "theta cells" are inhibitory interneurons (Ylinen et al., 1995b; Sík et al., 1995).

73. O-LM interneuron-supported thetalike oscillation *in vitro* does not require AMPA receptor-mediated excitatory postsynaptic potentials or acetylcholine and it is most pronounced in the CA1 region (Gillies et al., 2002). Computer modeling suggests that mutual connections between the O-LM and putative basket neurons are sufficient to sustain the oscillation. The key element in the model oscillation is the hyperpolarization-induced rebound discharge of O-LM neurons (Rotstein et al., 2005). A potential caveat is that, in the HCN1 knockout mouse in which I_h is virtually absent in hippocampal neurons, including O-LM cells, the amplitude of theta is *larger* than in the control littermate (Nolan et al., 2004). Distal dendrites of pyramidal cells contain the highest density of HCN 1 channels (Magee 2000; Lõrincz et al., 2002). Nevertheless, in the presence of I_h, O-LM cells can support theta oscillations.

74. The voltage activation range of I_h and I_m channels is close to the resting membrane potential; therefore, they are expected to enhance inhibitory and excitatory inputs at a frequency determined by the channel inactivation time constant. The opposing force of these channels is likely the persistent Na^+ current I_{NaP} (Pike et al., 2000; Hu et al., 2002).

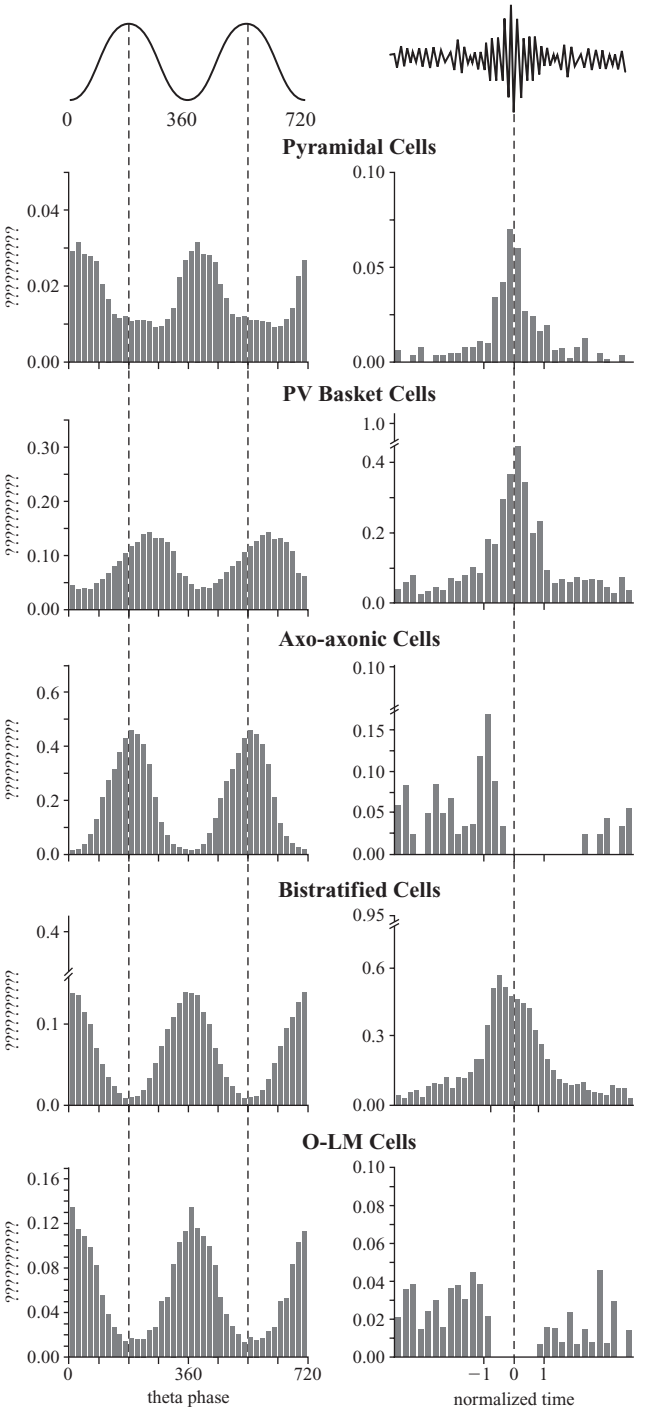

Figure 11.13. Timing of principal-cell action potentials is secured by a coordinated action of interneuron classes. Mean firing probabilities of pyramidal cells and different interneuron types during theta (left) and sharp wave-related fast "ripple" oscillations (right). Different constellations of interneuron classes contribute specifically and differentially to theta and ripple oscillations. Reprinted, with permission, from Klausberger et al. (2003, 2004).

time period. Single-cell properties perfectly match circuit features in both principal cells and interneurons. As a result, the multiple theta oscillation mechanisms can contribute to the computational properties of hippocampal–entorhinal neurons in complex ways. Of course, the exact details of this last statement are what we are most interested in, because these details determine how cell populations are assembled to represent episodes and maps. But first, let us examine how theta currents emerge.

Generation of Theta Oscillation Currents

Theta currents arise primarily from the laminarly arranged pyramidal cells and granule cells, simply because of majority rule. Theta currents have been most extensively studied in the CA1 region.[75] The first important observation was that the phase of the extracellularly recorded theta waves reverses gradually from the cell body layer to the distal apical dendrites without a prominent null zone. This behavior is a telltale sign of multiple, phase-shifted dipoles in action. The presence of multiple dipoles is not so surprising because every pathway with phase-locked activity to the global rhythm contributes to the extracellular mean field by its synaptic action on hippocampal neurons, and there are many paths to choose from. The largest amplitude theta is observed at the distal apical dendrites of the CA1 pyramidal cells, the layer where the afferents from layer 3 entorhinal cortical cells and the thalamic reunions nucleus terminate. The entorhinal cortex/reuniens–mediated theta, to a large extent, is NMDA-receptor dependent. Layer 2 grid cells provide rhythmic dipoles to the granule cells and the distal apical dendrites of CA3 pyramidal neurons. However, removal of the entorhinal inputs does not eliminate all theta. A rhythmic current sink remains in the mid-apical dendritic zone of CA1 pyramidal cells, a reflection of the CA3 theta output, and another dipole remains in the stratum lacunosum-moleculare, perhaps reflecting the inhibitory actions of the O-LM interneurons. Intrinsic conductances can further enhance the synaptic currents. Anita Kamondi, in my laboratory, recorded from thin dendrites of CA1 pyramidal neurons in the intact animal and found large-amplitude, high-threshold Ca^{2+} spikes phase-locked to the theta rhythm. These nonsynaptic transmembrane currents in active neurons should also contribute to extracellular theta.[76]

A further complication is that each set of excitatory terminals is matched by a family of interneurons (Cycle 2). The partner interneuron group of the entorhinal–reuniens input to the distal dendrites of pyramidal cells is the O-LM cells. By a feedback action, an active CA1 place cell can potentiate its O-LM interneuron(s), which in turn can prevent both synaptic excitation and Ca^{2+}-spike–mediated depolarization of the distal dendrites of neighboring pyramidal cells: a "winner-take-all" scenario. The CA3 excitatory input is matched by the bistratified in-

75. For a review on theta current generation summarizing progress and outstanding issues, including the most critical references on the topic, see Buzsáki (2002). A comprehensive experimental report on theta currents, including direct current (DC) measurements, is Brankack et al. (1993).

76. Upon strong dendritic depolarization, the voltage-dependent intrinsic oscillation can be faster than the ongoing network theta rhythm (Kamondi et al., 1998).

terneuron family. Both the dendrites and the extensive axon collaterals of these cells are confined to the oriens and radiatum layers, the target zones of the CA3 pyramidal cells. The basket family of interneurons also appears critical because they fire rhythmic bursts of spikes at theta frequency, thereby inducing inhibitory currents in the perisomatic region. Although these and nearly all other interneuron types are entrained to the rhythm, their maximum activity referenced to the phase of the theta cycle differs systematically, as our collaborative work with Thomas Klausberger and Peter Somogyi has shown.[77] It is hard to imagine how such an elaborate phase scheme would arise from a centralized septal pacemaker alone. The multiplicity of the theta current generators may also explain why previous "lumped" models, using a single "representative" neuron, have failed to account for the many facets of theta oscillations. Network models, which include intracellular properties of the constituents, have yet to emerge because they require information about the instantaneous firing patterns of the neurons contributing to the extracellular field.

Place-Cell Firing Is Phase-Guided by Theta Oscillations

If theta activity is the macroscopic correlate of behavioral navigation, and if hippocampal pyramidal cells generate internal maps for the animal, one might suspect that there is a link. Although several laboratories found a quantitative and reliable relationship between cell firing and theta phase using long recording epochs, these studies did not explicitly deal with place cells. On occasions, when I have consulted O'Keefe on the matter, he assured me that there is no relationship between theta waves and place-cell activity, or at least he cannot see one. In fact, the faster a place cell fires, the more likely that one can see spikes on every possible phase. The vague explanation was that strongly activated place cells could perhaps somehow escape from the enslavement to the common rhythm. Or perhaps the two phenomena, place-cell firing and theta oscillations, may signal different meanings. After all, landmark navigation by triangulation does not need a time metric. There was no immediate solution, and theta field and place-cell studies continued to be investigated independently in different laboratories.

At the same meeting where Ranck unveiled his newly discovered head-direction cells, a discussion was dedicated to the different types of theta oscillations. There were two candidates: cholinergic theta, which we equate today with the intrinsic CA3 theta generator, and the noncholinergic theta, corresponding to the entorhinal cortex–mediated large-amplitude oscillation. In the course of the discussion, O'Keefe suggested that perhaps we should

> speculate about the possibility that in fact there are various phase relationships that can occur between these two EEG patterns, and may be part of the function of the

77. Csicsvari et al. (1999) and Klausberger et al. (2003, 2004).

> EEG is to create interference patterns as a function of the different phases of these two theta waves. This might be a beginning to examine the function of these theta waves.[78]

Nine years later, he cracked the puzzle. O'Keefe's insight was that the interference of two oscillators beating at slightly different frequencies but acting on the same neurons can systematically affect spike timing. He and his student Michael Recce provided experimental support for the hypothesis by showing that the spikes of a place cell shift systematically relative to the phase of the ongoing theta oscillation. They called the phenomenon "phase precession."[79]

O'Keefe was right all along. Spikes of single place cells can occur at virtually any phase of theta.[80] However, such a wide phase distribution is not due to random noise, because there is a unique and systematic relationship between spikes and theta phase. As the rat enters the field, the spikes occur near the peak of theta waves, recorded at the CA1 pyramidal layer, and the spikes may retard a full cycle as the animal passes through the entire receptive field of the cell. As a result, the phase of spikes and the animal's position on the track are correlated. The firing rate behaves differently. The rate of single place cells is not an explicit marker of position, because it is confounded by the gain of locomotion velocity. Furthermore, rate increases and decreases as the animal moves in and out of the field. In contrast, the phase of the place-cell spikes shifts monotonically as a function of the rat's position on a linear track. The relationship between position and spike phase, also called "slope of phase precession," is independent of firing rate or the speed of the animal and depends only on the size of the place field. Ideally, the slope is a line between the beginning and end of the place field, spanning 360° of phases. The asymmetric nature of phase precession is therefore qualitatively different from the plane-symmetric firing rate distribution.

78. Buzsáki and Vanderwolf (1985), p. 386.

79. See general discussion in Buzsáki and Vanderwolf (1985). The discovery of phase precession is described in O'Keefe and Recce (1993). Unknown to these authors, an analogous phenomenon, error precession, had been described previously. Dunlap (1910) reported that when subjects had to syncopate in synchrony with a metronome, the timing errors tended to occur in advance of the next beat. The errors grew systematically until a correction occurred. Dunlop attributed the error precession to a frequency mismatch between stimulus and response, not unlike the two-oscillator interference model of O'Keefe and Recce. More recent experiments by Chen et al. (1997; 2001) demonstrate that timing errors are characterized by a $1/f^{\alpha}$ type of power law. The authors suggest that the $1/f^{\alpha}$ type of long-range correlated timing errors reflect distributed neural processes acting on multiple time scales. Another phase precession example is the relationship between temperature and the sleep/wake cycle. Analysis of sleep durations of volunteers isolated in caves or windowless rooms showed that free-running sleep/wake patterns obey a simple rule: the phase of the circadian temperature rhythm at bedtime correlates with the lengths of both prior wake and subsequent sleep phases (Strogatz et al., 1986). Since the two oscillations are slightly different in frequency, sleep times shift systematically along the temperature phase.

80. Below, I discuss how, although spikes can occur at any phase, spike density is highest at the trough of the theta cycle, signaling the middle of the place field. If theta is conceived as an order parameter of assembly activity, the trough serves as an attractor.

The phase-precession demonstration was the first convincing example of the long-suspected temporal "code," and it has remained the most compelling evidence in support of the critical role of oscillations in brain function. The possibility of a causal relationship between the timing of spikes and overt behavior spawned dozens of computer models exploring possible mechanisms.[81]

With the discovery of phase precession, timing directly entered the field of place-cell research, offering the opportunity to combine space and time in the service of episodic memory. Surprisingly (at least to me), O'Keefe has regarded the phase precession phenomenon as yet another piece of evidence in support of the allocentric, map-based theory of the hippocampus, even though omnidirectional place cells are not observed in the one-dimensional linear track, the apparatus in which the phenomenon of phase precession was discovered. He suggests that firing rate is not critical for place coding, making the liberated rate dimension available for coding something else, such as episodic memory.[82] Paradoxically, in the proposed dual coding scheme, time (phase) is assigned to map-based navigation, which does not need it, whereas timing is taken away from episodic memories, which do.[83] Below, we try to address this paradox and find some common grounds for navigation in rats and episodic memory in humans.

81. Phase is a relative variable, an abstract relational quantity that can be realized by many different effector systems. Relative phase may be used for the cooperation/integration of similar and segregation of dissimilar assemblies. Of course, in the physical world, it is time, not the abstract phase, that matters. For an exhaustive list of phase precession models, see Zugaro et al. (2005). Perhaps the first investigator to exploit phase as a coding mechanisms was Bernstein (1967), who emphasized that performance of any kind of complex movement can result from an infinite variety of possible combinations of the several hundred neuromuscular and skeletal elements. E.g., we can utter comprehensible sentences with our mouth full or one side of the face anesthetized after leaving the dentist office, using entirely different combinations of muscles than we normally do. His engineering solution to the problem of infinite complexity was self-organization of the neuronal pools aided by oscillatory patterning of motor units. The oscillation can serve as a temporal coordinator for the sequential activation of different muscle groups that are active during different phases of the cycle.

82. In light of what we know about the mechanisms of theta field generation by cell assemblies, it is hard to envision how rate and phase could be independently manipulated (Hirase et al., 1999; Harris et al., 2002; Mehta et al., 2002). If rate changed completely independently of the phase, it is difficult to explain the relationship between membrane polarization, spiking, and the generation of the extracellular mean field (see Buzsáki, 2002).

83. The evolution of this view (Huxter et al., 2003) is interesting because, in the original treatment of the subject (O'Keefe and Nadel, 1978), the authors considered the possibility that the addition of time to the spatial map in humans can provide the basis for an episodic memory system (see also Nadel and Eichenbaum, 1999), but this was rejected subsequently. "I reiterate the basic tenet of the cognitive map theory that the processing and storage of spatial information is the primary and perhaps exclusive role of the hippocampus in the rat, and that the data that appear to contradict this have been misinterpreted" (O'Keefe, 1999, p. 353). A convenient but disputable way to settle the issue would be the declaration of species differences of hippocampal computation, as is implicit in the quote. I view these things differently. Perhaps the most interesting and challenging question in this field is how a given physiological mechanism that evolved in a small-brain animal (e.g., navigation in physical space) can be exploited for more complex tasks in humans (e.g., memory storage and retrieval).

Sequence Coding by Theta Phase Ordering of Neuronal Assemblies

The simplest form of dead-reckoning navigation is moving along a straight line, for example, sailing from Genoa to Valencia and back or running back and forth on a linear track for a food reward. Since there are no junctions, there is no need for maps or omnidirectionally (explicitly) discharging place cells. Indeed, because omnidirectionality of place cells is the hallmark of landmark navigation, the unidirectional nature of hippocampal neurons on linear tracks and the running wheel can be taken as evidence for the lack of map formation in one-dimensional tasks.[84] On the other hand, coding for ordered locations and distances is analogous to learning an episode of sequentially presented or visited items. Both location sequences on a linear track and episodic sequences of arbitrary items are unidimensional; therefore, position relations correlate with temporal relations. The ordered locations and their distances can be computed from the theta period and the velocity-dependent firing rates of hippocampal neurons.

In human subjects, episodic memory performance is tested by subsequent free recall.[85] In the absence of access to free recall in animals, one can investigate the parallel between episodic learning and behavior in animals only by comparing the defining features of free recall and the neuronal correlates of dead reckoning on a linear track. As discussed above, free-recall tests indicate that stronger associations are formed between stimuli that occur near each other in time than between those that are separated by a greater interval; this relationship also holds for higher order distances. Furthermore, forward associations are stronger than backward associations. If these features are revealed in the relationship of hippocampal cell assemblies, they may be used to support the view that the neuronal mechanisms of episodic memory and dead reckoning are analogous.

In support of the above hypothesis, there is an important phenomenon embedded in the systematic phase relationship of place-cell spiking to the theta cycle. Place cells have long and heavy tails, the consequence of which is that spikes of many neurons often overlap in time. During successive theta cycles, multiple neurons, representing overlapping place fields, shift together in time and sustain a temporal order relationship with each other so that the cell that fires on the earliest phase represents a place field whose center the rat will reach first (figure 11.14). At a constant running velocity, the spatial position of the animal is

84. Bidirectional neurons are present occasionally in one-directional environments, e.g., at the corners of a rectangular track (Dragoi et al., 2003) or if objects are placed on part of the track (Battaglia et al., 2004). Corners and objects may elicit lateral turns and therefore multiple viewings of the same position, which can give rise to junctional (omnidirectional) neurons.

85. There is another procedural difference. In a free-recall task, human subjects sequentially inspect items in a single trial and are asked to repeat them in a later session. In contrast, rats on a linear track are tested repeatedly.

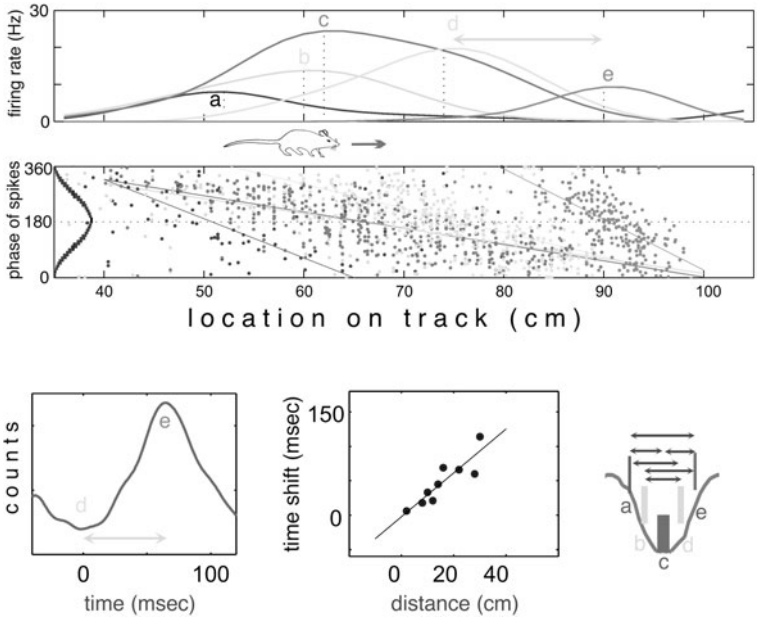

Figure 11.14. Representation of spatial distances by temporal correlation between spikes of hippocampal neurons. Top: Mean firing rate changes of five place neurons (a–e) as the rat traverses sequential locations on an elevated track. Middle: Spikes of each neuron during the same travels as a function of location (x-axis) and the phase of the theta cycle (y-axis). Note that for all place cells the highest firing rates occur on the trough of the theta cycle (180°). Lower left: Temporal correlation between neurons d and e. Note that the maximum rate of discharge of neuron e occurs approximately 60 milliseconds after the reference spikes of neuron d. Lower middle: relationship between distances between place field peaks (e.g., d and e in top panel) and temporal delays (e.g., d and e in lower left panel). Note that distances between place fields correlate with the temporal delays between spikes of the respective place cells. Lower right: Within theta cycles, the temporal order relationship of neurons represents place field differences. This temporal "compression" mechanism allows for the strengthening of synapses not only between neurons representing adjacent places but also nonadjacent (higher order) relationships. Reprinted, with permission, from Dragoi and Buzsáki (2006).

correlated with both the firing rate of a given place cell and the phase of spikes within the theta cycle. Therefore, the spike phase in a given cell provides an estimate of the distance traveled from the beginning of the place field. However, this distance information varies from cell to cell, since the slope of the phase precession depends on the size of the place field of the neuron. Thus, the distances between sequentially visited places cannot simply be calculated from the phase precession slope of individual place cells. Some other mechanism is needed for distance computation.

Taking two or more place cells into consideration, the distances between adjacent place field peaks can be estimated from the temporal relationship of the

corresponding neuronal spikes at two different time scales. The first scale is trivial and corresponds to the time it takes the rat to traverse the distances between place field peaks, defined by the maximum firing rate of each place cell in its field center. However, there is also a shorter or "theta period scale," at which the same distances are represented by the temporal relations of spikes at the tens of millisecond time scale. In essence, the place field sequences on the one-dimensional track are "compressed" into time/phase sequences of the theta oscillation.[86]

The discovery of the temporal coordination of neuronal spikes by theta oscillations offered new insights into the assembly functions of hippocampal neurons. William Skaggs and Mayank Mehta, working in the laboratory of McNaughton and Carol Barnes, suggested that the spike timing relationship of neurons, representing successive positions in the linear track, was just perfect for the short time window needed for spike-timing–dependent plasticity.[87] According to the spike-timing–dependent plasticity rule, a strong suprathreshold synaptic input always increases the synaptic strengths of subthreshold inputs that have occurred a few tens of milliseconds earlier. The plasticity rule, together with the sequential activation of neurons within the theta cycle, may be the key for tying together sequential places and items into meaningful episodes. How this may happen is discussed next.

Mechanisms of Theta Phase Precession

Transient phase coupling of two or more oscillators with different frequencies is an effective method for producing a continuously moving phase vector. As I have shown above, the discovery of phase precession in hippocampal place cells also sprang out from the idea of two interfering oscillators, tentatively identified with the entorhinal input (noncholinergic) and the intrahippocampal CA3 (cholinergic) theta oscillators. However, interference of two harmonic oscillators can explain phase precession only of single spikes. For the increased neuronal firing as a function of position within the place field, an additional mechanism is needed. Furthermore, the simple interference mechanism would also suggest that the properties of the global oscillators similarly affect the phase-locking of all place cells, with the consequence that all place cells have the same phase precession slope. This is not the case. The slope, the correlated place field size and the firing rate vary considerably among neurons.

A refined version of the dual-oscillator model operates at a single-cell level, where a transient dendritic depolarization from spatial inputs produces a

86. Skaggs et al. (1996) pointed first to this time-compression mechanism. The original version of this paper was rejected by the *Journal of Neuroscience,* due to an unfavorable review by one of the referees. Ironically, the original manuscript by O'Keefe and Recce (1993) was also rejected. It did not matter. Both papers, eventually published in *Hippocampus,* became highly cited pieces.

87. Although this notion is also presented in Skaggs et al. (1996), Mehta et al. (1997) provided specific experiments, and Blum and Abbott (1996) modeled how spike timing can be exploited for sequence coding.

voltage-dependent oscillation at a frequency slightly faster than the general somatic pacemaker theta input.[88] The predictions of the hypothesized "single-cell pacemaker" model is that neurons with stronger spatial inputs oscillate faster and therefore have steeper phase precession slopes and smaller place fields. A corollary prediction is that neurons with stronger dendritic excitation should discharge at a higher rate, resulting in a correlation between firing rate and the magnitude of spike phase advancement.[89] In the hypothetical single-cell oscillator model, the slope of phase precession of place cells depends only on the magnitude of the external spatial inputs. If place cells are sequentially activated on the track, a direct consequence of the single-cell model of spike phase precession is the theta–time-scale temporal correlation between neuron pairs with overlapping place fields.[90] Because no interactions among neurons are needed in this simple model, the "ideal" phase precession slope for a given place cell in any given trial would be that of the average slope across all trials. Deviation from this average in a particular trial can be attributed to some unaccounted "noise."

A different way of thinking about the theta–time-scale correlation among neurons is that sequential positions on the track are represented by unique sets of cell assemblies, and phase precession of spikes is a result of temporally coordinated activity within and between anatomically distributed groups of sequentially activated cell assemblies. At the very least, the synaptic interactions among neurons should account for the trial-to-trial variability of phase precession. An analogy may be helpful here to illustrate the differences between the pacemaker and cell assembly models. Imagine musicians of an orchestra playing their parts in isolation, supervised by a metronome timer only. Once all the musicians have played their parts separately, the recorded pieces are combined into a single set. I do not

88. Our intradendritic recordings from CA1 pyramidal cells *in vivo* provided the experimental basis for this hypothesis. Strong intradendritic depolarization by a voltage ramp of about 1 second, mimicking the dendritic depolarization of the place cells as the rat approaches the center of the field, produced voltage-dependent oscillations in the dendrite slightly faster than the ongoing field theta rhythm (Kamondi et al., 1998). However, models based on interference of oscillations predict that if one or both oscillators are reset, it should lead to an interruption of phase precession. This is not the case in the hippocampus. Single-pulse electrical stimulation of the CA3 collaterals resets the phase of the theta cycle and silences all hippocampal neurons for about 200 milliseconds. If such pulses are delivered while the rat is passing through a place field of an assembly, the recovered spikes occur on the phase of the theta cycle as in control runs (Zugaro et al., 2005). This could occur because the nondisturbed grid cells in the entorhinal cortex, coding for the previous position of the rat, can initiate the readout sequence determined by the dynamics of the CA3 recursive network (described further below). Moser et al. (2005) conducted a similar theta perturbation experiment, although phase recovery of place cells was not explicitly examined.

89. Kamondi et al. (1998), Harris et al. (2002), and Mehta et al. (2002). The relationship between rate, theta phase precession, and field size would suggest that, on average, firing rates in the ventral hippocampus have lower firing rates and less steep phase precession slope than place cells in the dorsal hippocampus. However, the observation that neurons with small and larger place fields can occasionally be found next to each other indicates that mechanisms other than a simple extrinsic excitation must be at work.

90. This is explicitly stated in Skaggs et al. (1996) and implicit in most other models.

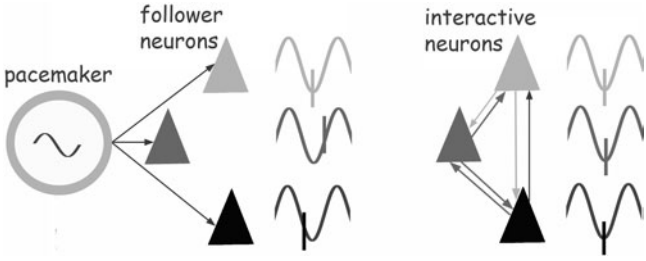

Figure 11.15. Temporal correlations can occur due to an external pacemaker or emerge from interactions among neurons. In the interactive ("orchestra without a conductor") case, temporal coordination among spikes can be more precise and better coordinated at a finer temporal scale.

have to convince the reader that the quality of the metronome-paced cut-and-paste piece would never match the quality of a real, concert hall performance, where interactions among musicians are available at a much finer time scale than supplied by the metronome-supplied beat (figure 11.15). Hippocampal neurons, like the members of the orchestra, are embedded in an interactive synaptic environment, and the timing of their action potentials is biased not only by theta oscillation pacing but also by all their synaptically connected and spiking peers.[91] A more radical view is that the interactions among the recurrently connected CA3 place cells give rise to rhythmic assembly discharges at theta frequency and that these assemblies coordinate neurons in the septum by way of the septally projecting long-range interneurons.

Functional interactions among place-cell peers offer the following hypothesis of the phase precession effect. The key idea is that sequentially activated cell assemblies in the hippocampus are connected by synaptic links, and the strengths of these synapses are reflected by the temporal relations between them.[92] George Dragoi, a graduate student in my laboratory, designed and conducted experiments to test the coordinated place-cell assembly hypothesis by recording from ensembles of hippocampal neurons simultaneously while the rat was walking clockwise or counterclockwise on a rectangular track. Distances between place field peaks of place-cell pairs on the track were correlated with their theta–time-scale corre-

91. In the synaptically connected assembly model, both external inputs and internal synaptic connections are important. Suppose that eight sequential environmental positions will produce similar depolarizing–repolarizing ramps, lasting for about 1 second, in groups of cells. The group with the same input is defined as an assembly. Upon depolarization, the groups oscillate slightly higher than theta frequency. As the rat passes the first position and approaches the next, the first oscillating assembly exerts a force (i.e., excitation) on the trailing assembly oscillator and advances its phase, etc. The synaptic strength between the assemblies determines the magnitude of the advancement (i.e., the time/phase difference within the theta cycle between members of successive assemblies). A conceptually similar spinal cord network explained the forward swim of the lamprey (Ermentrout and Kopell, 1994).

92. In the autoassociator model, distances in physical space are stored in the synaptic strengths among CA3–CA3 pyramidal neurons. Our analyses suggest that distance–time relations and, by extension, distance–synaptic strength relations are also present in CA3–CA1 synapses (Dragoi and Buzsáki 2006).

lation, a measure we called "sequence compression."[93] We exploited the observation that the trial-to-trial variability of phase precession of single neurons becomes larger after the rat leaves the center of the field compared to approaching it. Adding enough time jitter to the spikes emitted during the approach to the field center, we equalized the phase precession variability of individual neurons. This procedure therefore neutralized the contribution of the hypothetical intracellular oscillator in single place cells. Despite the added spike time jitter and the similar phase precession slopes, we found that the sequence compression (i.e., spike timing coordination among neurons) was still more reliable in the approach part than in the exit part of the place fields, supporting the idea that the "excess correlation" in spike times derives from either direct or interneuron-mediated synaptic interactions among members of the active assembly.[94]

Let me illustrate the same idea differently. Imagine that one could monitor the spiking activity of every neuron in the hippocampus, while the rat moves across the receptive field of a single place cell and its assembly members. Such a display would allow the observer to follow the evolution of multiple assemblies over time and identify all neurons that contribute to the representation of a single position or an episode item. The dot display of figure 11.16 approximates this imaginary population pattern. In the real experiment, instead of recording from all cells simultaneously, ensembles of neurons were recorded from several animals over multiple sessions, and all place fields were superimposed to represent an "average" receptive field.[95] The large X at zero time lag and zero distance corresponds to the occurrence of spikes of the reference neurons at the peak of their place fields (i.e., zero distance) averaged over multiple trials. The small dots correspond to the averaged time-spatial position occurrence of spikes of the partner neurons. The most important aspect of the illustration is that a given position is not simply defined by the time-discrete discharge of a cell group. Instead, the representation evolves and dissolves over time. Seven to nine "clouds" can be recognized, with centers separated by 110–120 millisecond intervals, related to the duration of theta oscillation. Spatial distances are repeatedly represented by the discharges of the partner neurons, beginning approximately 500 milliseconds before the animal reaches the center of the place and lasting for another 500 milliseconds until the rat exits the field. The accuracy of predicting the field

93. Compression of items into theta cycles is reminiscent of the mnemonic technique called "chunking." Chunking is best known in the task of memorizing a string of numbers in short-term memory. Typically seven (± two) "items" are chunked together (Miller, 1956). Adding tune and tempo to arbitrary sets of items is known to enhance memorization and has been exploited by school teachers for generations. Memorizing long strings of random letters, e.g., "SPWFMRITHETAAPEEGPETSFN" is easier if they are chunked into "SPW, fMRI, THETA, AP, EEG, PET, SFN."

94. Dragoi and Buzsáki (2006). The oscillatory dynamics-based temporal coordination among neurons is reminiscent of attractor-based dynamical models (Tsodyks et al., 1996; Wallenstein and Hasselmo, 1997; Samsonovich and McNaughton, 1997; Jensen and Lisman, 1998, 2005).

95. Because individual place fields vary in size, introducing noise to the superimposed fields, it is expected that the clouds would be much better segregated if all neurons in the hippocampus could be recorded simultaneously and displayed similarly during a single trial.

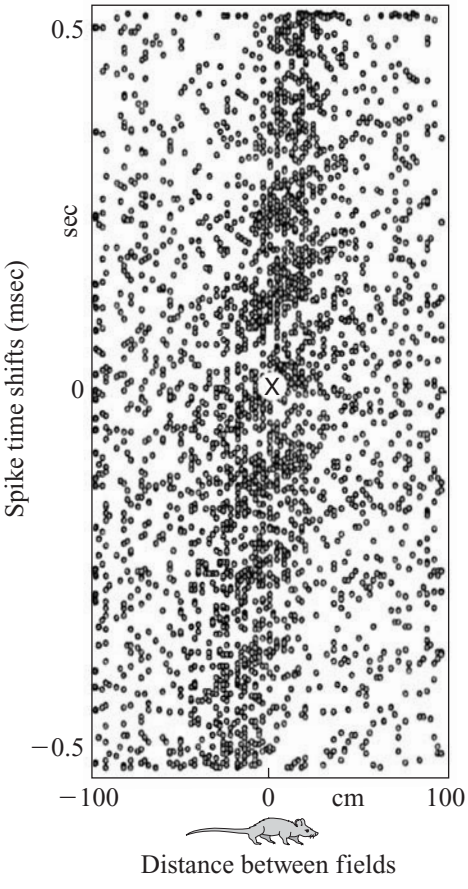

Figure 11.16. Temporal coding of metric distances by cell assemblies: discharge timing of partner neurons (dots) relative to the spikes of a chosen place cell in the middle of its field (X) as a function of the rat's travel. Time zero is the spike occurrence in the middle of the field. Note multiple clouds of dots, reflecting precise temporal representation of place field distances nested within the repeating theta cycles. Reprinted, with permission, from Dragoi and Buzsáki (2006).

center gradually increases in subsequent theta cycles as the animal approaches the center, corresponding to the densest central cloud. The spatial extent of the central cloud is 30 to 40 centimeters, which reflects the mean size of a place field in the dorsal hippocampus and the grid size of the neurons in the dorsomedial entorhinal cortex.

Because the average walking velocity of the rat on the track is 30 centimeters per second, corresponding to approximately 5 centimeters of travel per theta cycle, shifting parts of the same field are repeatedly and intermittently represented by the same groups of cells in six to nine subsequent theta cycles. The neuronal sequences are direction specific because plotting the same reference spikes with

the same partner neurons on the opposite journey on the track does not show comparable clouds.

Due to the long and heavy tails of the place fields, several place cells are active in each theta cycle, but the assembly composition varies from cycle to cycle. The whole extent of the field is represented only once in the central cycle, surrounded by place cells of past and future positions. This complex representation of positions and distances by the evolving and dissolving cell assemblies can be elucidated by the following example. When looking out of the window of a moving train and fixating on distant objects as they move past, one makes successive rapid eye movements parallel with the direction of the motion of the train. Between the fast eye moments, shifting but overlapping sceneries will be repeatedly surveyed. In each scanning eye movement, a new segment of the scenery is included, overlapping with the previous segment. Similarly, assemblies in the hippocampus take overlapping snapshots of approximately 30–40 centimeters of space in each theta cycle. The neurons that contribute to the definition of the current position are also parts of assemblies representing past and future positions. The temporal relationship of cell assemblies over multiple theta cycles is an advantageous mechanism for strengthening the synaptic connections between the evolving assemblies.

A remarkable outcome of the assembly organization is that the relationship between successive positions on the track and the theta phase-related discharge of place cells (i.e., the slope of phase precession) remains the same independent of the locomotor velocity of the rat. The constant relationship is made possible by the velocity-dependent gain of place-cell discharge frequency (figure 11.17). To illustrate this, let us assume that on two successive trials the rat traverses the place field of the recorded neuron in 1 second and in 0.5 second. In the first, slow run, the place cell will be active in eight theta cycles, but only in four cycles in the second faster run.[96] However, during the faster run, the place cell is more strongly depolarized and the number of spikes per theta cycle may double because the velocity-dependent gain. As a result, the phase shift of spikes from cycle to cycle is twice as large as during the slow run. In short, the velocity-gain compensates for the shorter time spent in the place field, leaving the relationship between phase and spatial position unaltered.

Complementary Roles for CA1 and CA3 Cell Assemblies

The representation of distances by theta–time-scale correlations is similar for CA1–CA1, CA3–CA3, and CA3–CA1 neuron pairs. Nevertheless, CA1 and CA3 assemblies show important differences. The most fundamental difference is that the discharge probabilities of the CA1 and CA3 populations alternate. CA1 cell assemblies are attracted to the trough of the local theta waves, whereas CA3 cell assemblies are most active on the opposite phase of the theta cycle. Because the

96. Although speed has some minor effect on theta frequency, this change is very small, so that doubling running velocity may increase frequency by only a few percent.

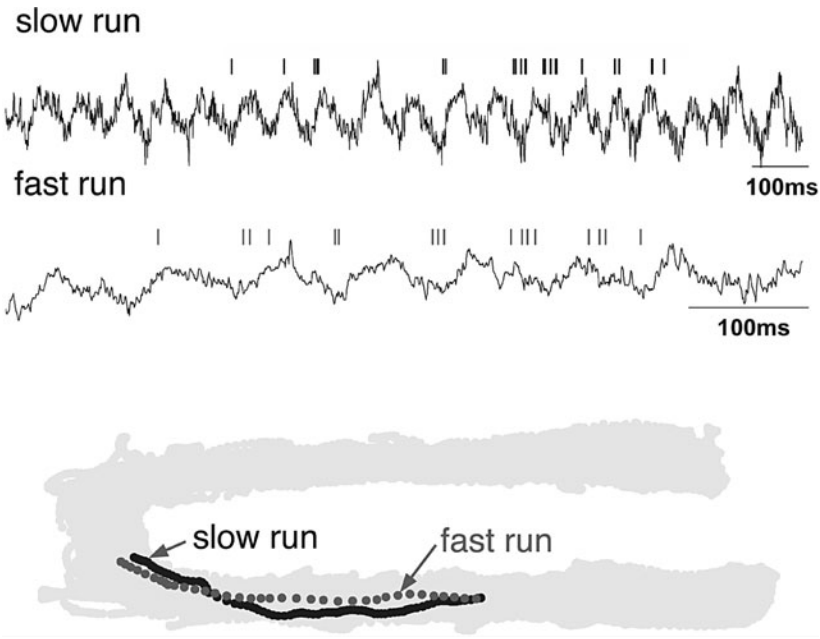

Figure 11.17. Velocity gain of place-cell discharge keeps the spiking phase versus position relation constant. Top: On fast and slow runs of the rat through the maze, the number of spikes emitted in the place field of the neuron is approximately constant, whereas the number of theta waves within the field is twice less during fast run than during slow run. As a result, the number of spikes per theta waves as well as the phase shift of spikes from one theta cycle to the next is larger during fast runs. Bottom: The rat's trajectory during the two representative runs. Dots correspond to the rat's instantaneous position within the place field. Courtesy of C. Geisler and G. Buzsáki (unpublished observations).

most numerous excitatory inputs to CA1 pyramidal cells are supplied by the CA3 collaterals, the antiphase discharge correlation of the two populations needs an explanation.

A reasonable approach is to examine the functional connections within the feedforward CA3–CA1 system and the distinct population dynamics of each region. The CA3 excitatory recurrent system is able to maintain self-organized activity, as illustrated by the emergence of thetalike oscillation in the isolated slice preparation. As recurrent excitation builds up, more and more inhibitory neurons are recruited, which limits and terminates the spread of excitation in the recurrent system. In other words, excitation and inhibition build up and die in a relatively parallel manner during the theta cycle in the CA3 region. The buildup of excitation and inhibition also gives rise to a transient gamma oscillation, associated with the increased gamma-cycle–locked oscillation of basket and chandelier cells, as Ole Paulsen and his colleagues at Oxford University, working *in vitro,* and Jozsef Csicsvari working in the intact hippocampus in my laboratory have

shown.[97] Of course, the axon collaterals of the same CA3 cell assemblies that give rise to theta and gamma oscillations also excite CA1 pyramidal cells.[98] The result is a temporally coherent increase of gamma power in both regions on the descending phase of the CA1 pyramidal cell layer theta, which is precisely the phase when the CA3 recurrent excitation reaches its maximum.

The observation of the antiphase discharge of the CA3 and CA1 cell population suggests that the simultaneously built-up CA3 feedforward inhibition prevents most CA1 place cells from discharging. As a result, CA1 neurons can discharge maximally when their perisomatic inhibition is weakest.[99] This may be the neurophysiological explanation for the abstract term "attractor" at the trough of the theta cycle. So what causes CA1 pyramidal cells to discharge, and what is the contribution of the CA3 input besides feedforward inhibition? At present, we do not have a full explanation, but several clues point to a possible answer. First, feedforward inhibition in the CA1 region is spatially much more widespread than the convergence of excitation from a given CA3 assembly. This is a useful mechanism for preventing the discharge of those CA1 pyramidal cells that do not receive convergent excitation from firing CA3 cells. Second, the major extrahippocampal input to CA1 neurons is the direct layer 3 entorhinal projection. This pathway has been implicated in determining the place-related activity of CA1 pyramidal neurons.[100] The third clue has been provided by Douglas Coulter and colleagues at University of Pennsylvania–Philadelphia. Using intracellular recording and optical imaging in the hippocampal slice preparation, they confirmed the well-known observation that electrical stimulation of the entorhinal input typically evokes hyperpolarization in CA1 pyramidal cells. However, when the entorhinal input was activated *after* stimulating the CA3 input, the hyperpolarization was converted into depolarization and discharge of the cell.[101] The optimal interval between the CA3 and entorhinal inputs for discharging CA1 pyramidal cells was 40–60 milliseconds, that is, precisely one half of the theta cycle. The implication is that an active CA3 assembly predicts the future location of the animal half a theta cycle earlier. If the layer 3 entorhinal input "confirms" the

97. Fisahn et al. (1998), Csicsvari et al. (2003), and Mann et al. (2005).

98. Chandelier cells may be activated in a similar manner (Klausberger et al., 2003). However, most apical dendrites of chandelier cells are confined to the stratum lacunosum-moleculare, so they may get less excitation from CA3 pyramidal cells than from basket neurons (Li et al., 1993).

99. The maximum discharge of CA1 pyramidal cells at the trough of local theta is also associated with the maximum activity of the O-LM interneurons, which are driven mainly by the CA1 place cells (Klausberger et al., 2003). The discharging O-LM cells and the inhibitory postsynaptic potentials their terminals produce in stratum lacunosum-moleculare may explain the presence of a current source at the time when place cells are active. This arrangement can contribute to the isolated activity of place cells. The winner place cell may prevent a neighboring neuron from discharging by activating the O-LM neurons in a feedback manner. The winner cell may continue to discharge because its perisomatic inhibition may be depressed by the release of endocannabinoids, which suppress GABA release from the inhibitory terminals (Klausberger et al., 2005).

100. Brun et al. (2002).

101. The conversion of inhibition to excitation in response to the entorhinal input is explained mainly by the transient activation of NMDA receptors by the CA3 collaterals (Ang et al., 2005).

prediction, the CA1 pyramidal cells will respond. If the prediction is not confirmed, the layer 3 input remains largely ineffective.[102] Overall, the combination of these observations suggests that the CA3 and CA1 systems operate as a functional unit during theta oscillation.

Physiological Definition of Spatiotemporal Context

Let us now synthesize the findings discussed so far into a coherent picture (figure 11.18). Distance information between positions on the linear track is stored by synaptic weights among neurons of the CA3–CA1 collateral system. During each theta cycle, this large synaptic space is searched, recalling several, temporally linked cell assemblies. The trajectory in the neuronal space represents the position sequences that the rat just passed and will traverse during the next half second or so. The internal sequence readout in the CA3 region is triggered by the previous locations by way of the active grid cells of the entorhinal cortex. The readout is forward in time, reflecting the sequence order during learning. In each theta cycle, the most active CA3 assembly occurs at the peak of the theta cycle referenced to the CA1 pyramidal layer and corresponds to the predicted current location of the rat's head.[103] As the CA3 assemblies dissolve, the CA1 assemblies get stronger, partially because of the decreasing perisomatic inhibition and because of the strengthening of the layer 3 entorhinal input, signaling the current location. The predicted and perceived locations are therefore replayed in tandem by the most active CA3 and CA1 assemblies, respectively.

As the animal moves forward, a new cell assembly dominates each theta cycle. However, the assembly members that define the current location also contribute spikes to the representation of the past and future positions in multiple theta cycles. Conversely, the most active CA1 assembly, anchored to the trough of the local theta, is flanked by spikes on the descending and ascending phases, contributed by assembly members of passed and upcoming locations, respectively, corresponding to the rat's locomotion trajectory on the track. Stated differently, information about places and distances is not determined simply by single

102. In support of this cooperative effect, Wilson and McNaughton (1993) described that, in a novel environment, CA1 pyramidal cells remain largely silent for several minutes. Furthermore, Nakazawa et al. (2002) showed impairment of place-cell activity when only a fraction of the original cues were presented to mice in which the NMDA receptor gene was genetically ablated specifically in CA3 pyramidal cells. In the experiments of Brun et al. (2002), place-cell activity in CA1 was observed after cutting most CA3–CA1 connections and removing both convergent excitation and feedforward inhibition. However, Brun et al. also emphasize that many features of the place cells (e.g., field size, dispersion) were quite different from the sharp place fields found in the intact animal. Recall of spatial information was also impaired in the CA3–CA1-disconnected rats.

103. Muller and Kubie (1987) also suggested that place-cell firing predicts future locations a few centimeters in front of the head of the rat.

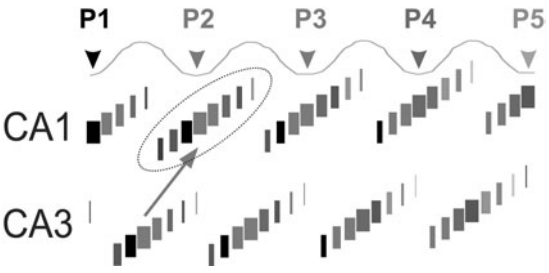

Figure 11.18. Definition of "context" by oscillatory timing of cell assemblies. The width of the bars indicates firing rates of the assemblies, and the temporal differences between assemblies reflect distances of their spatial representations. The predicted (CA3) and the environment-updated (CA1) representations (places P1–P5) are phase shifted. The current position of the rat's head is represented by the most active CA1 cell assembly at the trough of CA1 theta oscillation. This assembly is surrounded by the representation of past and future places within the same theta cycle, defining the spatiotemporal context for the most active assembly. Reprinted, with permission, from Dragoi and Buzsáki (2006).

assemblies bound to the troughs of theta oscillation but also by the precise temporal sequences within cycles. The sequences within theta cycles precisely reflect the past, present, and future place field centers of the sequentially active cell assemblies on the track.

In light of the above summary, we can conclude that the current position of the animal is embedded in the representation of the past and the expected future in terms of both location and time. In short, the currently coded item is placed into *spatiotemporal context* by the theta oscillation mechanism. This context dependence can explain why a hippocampal place cell, active on a journey in one direction, may not be active at the same location during the opposite journey.[104]

Navigation in Real and Memory Space

After navigating through decades of research on hippocampal single cells and theta oscillations, and defining context by a physiological mechanism, we now return to the problem of memory. As discussed above, work in humans suggests that the hippocampal–entorhinal system is involved in both episodic and semantic memories. Both types of memory can be verbally declared because they are parts of the "conscious brain systems." Research on animals, on the other hand, has

104. A prediction of the hypothesis that context is defined by the spatiotemporal sequences of neuronal assemblies is that changing the synaptic strength among neurons should change their sequences on the track. In support of this prediction, artificial alteration of synaptic weights by long-term potentiation affected both place fields and distance representation by neuron pairs (Dragoi et al., 2003).

implicated the hippocampal–entorhinal system in either dead-reckoning or map-based navigation. The challenging issue is to understand how a useful neuronal mechanism that evolved in a small-brain animal (e.g., navigation in physical space) can be exploited for another purpose (e.g., memory storage and retrieval) at later stages of brain evolution.

Relationship between Episodic Memory and One-Dimensional Travel

Let me recapitulate briefly the discussion on dead-reckoning and landmark navigation. In dead reckoning, the distances passed are calculated on the basis of self-generated cues rather than environmental inputs. This process does not require repetition. In contrast, map-based navigation requires external cues or at least their internal representation and is learned by repeated visits to the same positions. These different strategies can be studied best in one-dimensional and two-dimensional environments. The prerequisite for forming a map is junction crossings, that is, visits to the same positions from different directions, which is ideal in two-dimensional environments.[105] It follows that dead-reckoning exploration must precede the establishment of a map. At the neuronal level, the distinction between the two forms of navigation is illustrated by the unidirectional and omnidirectional place cells in one-dimensional and two-dimensional environments, respectively.[106] Omnidirectional place cells explicitly define particular positions and do not require temporal context or self-reference.[107] How do these forms of navigation relate to memory?

In one-dimensional tasks, representation of the ordered locations and their relationships is achieved by encoding metric information about distances in space and direction of movement. This process is analogous to learning an episode of sequentially presented or visited items. The difference lies in the

105. As discussed above, a map can be generated without vision, as well, in which case each place must be physically visited. With vision, it may be sufficient that the eye "visits," i.e., explores, every place.

106. An alternative view of the episodic memory vs. mapping-based navigation dilemma is that the hippocampus is a more general system, concerned not only with spatial maps but also with many other types of nonspatial relations. Howard Eichenbaum at Boston University makes the point that the spatial map is simply a byproduct of a relational memory system. Relations can be either temporal or spatial. Eichenbaum designed behavioral experiments in which the relations between spatial or nonspatial stimuli had to be memorized, and he demonstrated that animals with hippocampal damage were consistently inferior in solving such tasks (Bunsey and Eichenbaum, 1996). According to the relational hypothesis, individual hippocampal neurons code for sensory cues of any type, other subsets for their combinations, and yet other groups of cells for relations, including temporal (Wallenstein et al., 1998; Hampson et al., 1999; Eichenbaum, 2002). However, learning general relations requires repetition, and the temporal context is optional. In contrast, the essence of episodes is their spatiotemporal context, and they can be acquired by a single exposure.

107. Because omnidirectionality of place-cell firing is the hallmark of landmark navigation (O'Keefe and Nadel, 1978), the unidirectional nature of hippocampal neurons on the linear track can be taken as evidence of the lack of map formation in one-dimensional tasks.

nature of the *inputs* rather than the nature of hippocampal computation. An ideal structure for episode coding and recall is an autoassociator, since free recall is essentially a pattern-completion problem. The asymmetric nature of the recursive CA3–CA3 and CA3–CA1 connections, combined with temporal ordering of cell assemblies and spike-timing–dependent plasticity, favor temporally forward associations. Similar to the physical distances on the linear track, positional "distances" among items of an episodic list can be coded by the synaptic strengths between the cell assemblies, which represent the items. Because distance representations are brought together into the cycle time of theta, not only temporally adjacent but also noncontiguous items can be linked together by synaptic plasticity. These higher order links can be established because the probability of anatomical connections among any cell pairs is similar in the hippocampus. Therefore, it is the timing rule of synaptic plasticity that functionally connects assembly A more strongly to assembly B than to assembly C in the sequence (see figure 11.14). However, if for some reason assembly B cannot be recalled, the excitation spreads toward the next best-connected assembly, which is C.

In humans, performance is tested by later free recall, in the absence of external explicit cues. This recall can occur if the most active cell assembly in a given theta cycle, encoding the remembered item "calls up" the next best-connected assembly, which also reflects the order of the learned sequence. Due to the lack of access to free recall in animals, this critical feature can be examined only indirectly by comparing the fundamental features of free recall and neuronal correlates of behavior.[108] However, on a linear track, environmental cues constantly supervise and affect the direction of activity sequences by updating the content of each theta cycle, similar to cue-guided story-telling of episodes.[109] In contrast, spontaneous or free recall requires that the cell assembly sequences of subsequent theta cycles be advanced by the content of the previous cycle rather than by external cues. Supporting this possibility, we observed spontaneous changes in firing rate and associated phase precession of place neurons while the rat was running in a wheel with its head staying stationary.[110] Because environmental and self-motion cues were kept constant, such "spontaneous" phase precession could have been brought about by shifting cell assemblies in successive theta cycles. These internally generated sequences can be potentially regarded as neuronal correlates of episodic recall.

108. Fortin et al. (2004) used such an approach in recognition memory and found a striking similarity between behavioral choice patterns in rats and humans.

109. This external "updating" mechanism is best demonstrated by the recurrence of spikes reflecting the correct position of the animal after transiently silencing hippocampal networks (Zugaro et al., 2005).

110. Such spontaneous phase shifting of spikes is rarely observed during running but is a common in REM sleep (Harris et al., 2002). Most neurons in the wheel-running task sustain steady discharge rate, although some show phase-precession (Czurkó et al., 1999; Hirase et al., 1999).

Relationship between Semantic Memory and Spatial Maps

With the link between navigation in one-dimensional task and episodic memory established, let us turn to the relationship between spatial maps in two-dimensional tasks and semantic memory. As discussed above, place cells in one-dimensional travel have unidirectional place fields, determined primarily by the position sequences passed. This situation changes dramatically if paths of the navigation cross, as happens routinely during exploration. Now the activated neurons at the crossroads will be tied to different routes or episodes.[111] The establishment of such junctions and the emergence of omnidirectional place cells mark the emergence of a map. The omnidirectionality of place cells can therefore be taken as evidence that the rat approached a position or landmark from multiple directions. Omnidirectionality is thus an indication that the place cell has become part of multiple neuronal trajectories, and its activation no longer depends on a unique temporal sequence of particular cell assemblies. Once established, omnidirectional place cells no longer require a temporal context. They become explicit gnostic units.[112]

Applying the same idea to humans, multiple episodes with common junction items can free the common item from its context. If the same junction points of the episodes are traversed repeatedly by other episodes, they no longer require the temporal context of item sequences. For example, discovery of a new neuron type or a novel oscillation is an episode, reflecting a series of exciting and memorable events through space and time for those involved. However, after the observations are confirmed in multiple laboratories, the pioneers and the conditions of the initial discoveries become irrelevant and the convergent or joint elements of the research lose their spatiotemporal context and become scientific facts. Multiple overlapping observations with common junctions are therefore the source of semantic knowledge. Seeing a dog for the first time in life is an episode. However, after seeing many different dogs and pictures of dogs, the universal features assume a semantic meaning: a common name.[113] Neuron members of an omnidirectional or explicit assembly collectively define or symbolize the "meaning" of an item. Such explicit, higher order representation is invariant to the conditions that created it.

Although dead-reckoning navigation and episodic memory are requisites of landmark-guided maps and semantic information, storage of consolidated semantic knowledge may no longer require the large combinatorial associational network provided by the hippocampus.[114] Once maps and semantic information

111. A similar explanation for the multidirectionality of place cells was offered to by Eichenbaum (2002) and Brunel and Trullier (1998).

112. Such explicit representation by hippocampal neurons has been documented in humans, as well (Heit et al., 1998; Quiroga et al., 2005).

113. Computer models of categorization that learn via changes of connections work in essentially the same manner (McClelland et al., 1995). The categories generate a context that facilitates the retrieval of memories. E.g., if a list of items involving faces, locations, and objects is presented, during the recall process items in the same categories tend to cluster. There is no consensus yet on the mechanisms of semantic memories, and their episodic origin is debated.

114. For a more exhaustive discussion of this topic, see Buzsáki (2005b).

are solidified, they can be transferred to neocortical destinations. However, transfer of information needs another type of oscillation, which is discussed in Cycle 12.

Briefly . . .

The hippocampus is the ultimate search engine for the retrieval of archived information. In this Cycle, we examined how hippocampal theta oscillations are related to episodic and semantic memory, "dead reckoning" (or path integration), and "map-based" (or landmark) navigation. These concepts have been associated with the hippocampal–entorhinal system, primarily on the basis of lesion cases in humans and unit and field recording studies in smaller animals.

The hippocampus and associated structures are organized in multiple loops and are part of the allocortex, with reciprocal connections to the neocortex. The most prominent collective pattern of hippocampal neurons is theta oscillation, a sustained rhythm associated with explorative navigation. A consortium of circuit and single-cell properties supports theta oscillations, which provides timing for individual hippocampal pyramidal and granule cells and the principal cells of the limbic system. The major theta current generator in the hippocampus is the entorhinal input to the distal apical dendrites of CA1 pyramidal cells. Theta currents in this layer arise from at least three mechanisms. First, currents (sinks) generated by excitatory postsynaptic potentials are mediated mainly through NMDA receptors. Another sink is due to rhythmic, voltage-dependent Ca^{2+} spikes in the distal dendrites that occur in strongly excited neurons. Third, the discharging CA1 pyramidal neurons activate O-LM interneurons whose main axon arbors terminate in the stratum lacunosum-moleculare. These synapses set up inhibitory currents (sources) and compete with the effects of the excitatory entorhinal input on less activated pyramidal cells ("winner take all").

The medial septum is a key rhythm generator of theta cycles, but the recurrent CA3 system can also generate theta oscillations. Interactions between CA3 pyramidal cells and basket interneurons also give rise to gamma frequency oscillations, phase-locked to the slower theta rhythm. Inhibition and gamma power are built up simultaneously in the CA3 and CA1 regions, the consequence of which is that pyramidal cells in these sectors, on average, discharge on the opposite phases of the theta cycle. These various theta oscillation mechanisms are responsible for the temporal organization of pyramidal neurons.

The discharge pattern of single neurons depends mainly on the testing conditions. In one-dimensional tasks, such as a straight track, only dead-reckoning navigation is possible. Individual pyramidal cells on the track fire maximally at particular positions, signifying the place field center. In CA1 pyramidal cells, the spikes first occur on the peak of theta waves as the rat enters the field, fire maximally at the trough of the theta in the middle of the place field and continue the phase shift up to a full cycle after the rat leaves the receptive field of the cell. As

a result, the phase of spikes and the animal's position on the track are correlated. As the rat moves forward, a new cell assembly dominates each theta cycle. However, the assembly members that define the current location also contribute spikes to the representation of the past and future positions in multiple theta cycles. Conversely, the most active CA1 assembly, anchored to the trough of the local theta, is flanked by spikes on the descending and ascending phases, contributed by assembly member neurons of passed and upcoming locations, respectively, corresponding to the rat's locomotion trajectory on the track. Because of the long and heavy tails of the place fields, multiple cell assemblies are coactive in any given theta cycle. Distances between place field peaks of place-cell pairs on the track are correlated with their theta–time-scale correlation, so that information about successive metric distances is reflected in the precise temporal sequences within cycles. Because representation of the current position is embedded in the representation of the past and the expected future, the temporal compression mechanism of the theta oscillation objectively defines spatiotemporal context, a key ingredient of episodic memory.

Coding for ordered locations and distances is analogous to learning an episode of sequentially presented or visited items. Similar to the theta cycle representation of physical distances in one-dimensional tasks, positional "distances" among items of an episodic list can be coded by the synaptic strengths between the cell assemblies, representing the items of the episode. Because distance representations are compressed into the cycle time of theta, not only temporally adjacent but also noncontiguous items can be linked together by synaptic plasticity. These higher order links can be established because the probability of anatomical connections among cell pairs is similar in the hippocampus. The created links among cell assemblies may account for the contiguity and temporal asymmetry principles of episodic memory. An ideal structure for episode coding and recall is an autoassociator with a large random synaptic space, since free recall is essentially a pattern-completion problem. The extensive axon arbors of CA3 pyramidal cells and their recursive CA3–CA3 and CA3–CA1 connections are ideal for storing large numbers of episodic memories and for retrieving them efficiently.

In two-dimensional environments, exploration leads to crossing the same positions from different directions. These junctions serve to establish a map and subsequent landmark (map-based) navigation. The hallmark of the cognitive map is the presence of omnidirectional place cells in the hippocampus and tessellating "grid cells" in the entorhinal cortex. The omnidirectional discharge pattern in a neuron is an indication that the place cell has become part of multiple neuronal trajectories and that its activation no longer depends on a unique temporal sequence of particular cell assemblies. Once established, omnidirectional place cells no longer require a temporal context or self-reference. They explicitly define position.

Analogous to the dead reckoning–to–map transition in the rat, exemplified by the conversion of unidirectional to omnidirectional neurons, multiple

episodes with a common item can free the common item from its spatiotemporal context. Neuron members of an omnidirectional or explicit assembly collectively define or symbolize the semantic "meaning" of an item. Explicit representation is invariant to the conditions that created it. The short punch line of this Cycle is that episodic and semantic memory representations may have evolved from mechanisms serving dead-reckoning and map-based navigation, respectively.

Cycle 12

Coupling of Systems by Oscillations

> It is necessary to study not only parts and processes in isolation, but also to solve the decisive problems found in organization and order unifying them, resulting from dynamic interaction of parts, and making the behavior of the parts different when studied in isolation or within the whole. . . .
>
> —Ludwig von Bertalanffy, *Allgemeine Systemtheorie*

Hierarchical operations in the brain indicate not only that representations in "higher" centers are more complex and abstract than are lower areas, but also that such sequential, feedforward processing inevitably requires temporal delays. However, bottom-up and top-down distinctions are merely abstractions, a convenient way to conceptualize activity in brain circuits. In reality, a purely feedforward scheme is an exception in cortical systems; the typical connectivity is reciprocal and recurrent innervation. There is no real structural "top" in neuronal hierarchy since the higher order information in a brain area can be immediately forwarded back "down" to other areas. The top or end of computation is generally heralded by time, marked by inhibition of activity, rather than by some defined anatomical boundary. Neuronal information is propelled in parallel in multiple juxtaposed and superimposed loops, making the distinction between the top and bottom processing very difficult. For example, the psychological construct "attention" is often thought of as a top-down process, an intentional act, initiated in some hypothetical "executive" top-level areas. However, a candidate physiological mechanism of attention is gain control, which is a quantitative rather than qualitative change, reflecting an enhanced sensitivity of the processing circuits to inputs. Such enhanced gain in neuronal networks can be achieved mainly by subcortical neurotransmitters, such as acetylcholine and norepinephrine, which enhance cortical gamma

oscillations.[1] If these neurotransmitters are essential for the attention-associated gain of neuronal responses, the process is not simply a top-down instruction but a loop pattern.

As I have also shown, all cerebral cortical circuits of the mammalian brain can maintain an autonomous, self-organized activity, independent of the inputs. Thus, cortical activity is in perpetual motion, and every motor and cognitive act is a synthesis of self-generated, circuit-maintained activity and environmental perturbation, as discussed within the "brain in the body and environment" framework in Cycle 8.[2] Whereas the brain can detach itself from the body and environment to a large extent (e.g., during sleep), the converse—that is, invariant responses of the brain irrespective of its state—is true only for elementary reflexes involving short loops. In most situations, the brain's reaction to environmental changes is not invariant but depends on the outcome of previous reactions in similar situations and on the brain's current state, determined by the multiple interactions among the various oscillators. These recent views of brain function emphasize the constructive nature of adaptive neuronal operations.[3] If different brain areas and systems constantly generate their autonomous self-organized patterns, how can they initiate a conversation and listen to each other? I suggest that the fundamental basis of such communication and exchange of information is oscillatory phase-locking. In reciprocally interconnected systems, temporal ordering of neuronal activity by way of phase-locking can direct the flow of excitation. Neurons that discharge earlier can drive the neurons of the trailing oscillator (Cycle 4). By simply reversing the phase offset, the direction of drive can also be reversed. The main goal of this Cycle is to illustrate how network and system interactions can be assisted by oscillations.

Coupling of Hippocampal–Neocortical Circuits by Theta Oscillations

Because it is largely past experience that determines the brain's response to environmental inputs, it is expected that the dialogue between the hippocampus and the relevant parts of the neocortex is virtually continuous. Viewed from this context, it is not surprising that hippocampal theta oscillations are among the rare sustained rhythms in the brain (Cycle 11; figure 12.1). This continuous dialogue, in principle, can be accomplished in several different ways. The simplest and less likely scenario is that the phasic hippocampal output forces the neocortical assemblies to fire in phase with theta frequency. The second option is that hippocampal output drives

1. For the roles of neuromodulators in attention and information processing, see Foote et al. (1983), Metherate and Ashe (1995), and McCormick (1992). The role of the basal forebrain in enhancement of cortical gamma oscillations, see Jones (2005).

2. The concept of "situatedness" expresses this context-dependent synthesis (Varela et al., 1991; Thompson and Varela, 2001).

3. For thorough and comprehensive reviews of top-down operations, see Engel et al. (2001) and Miyashita (2004).

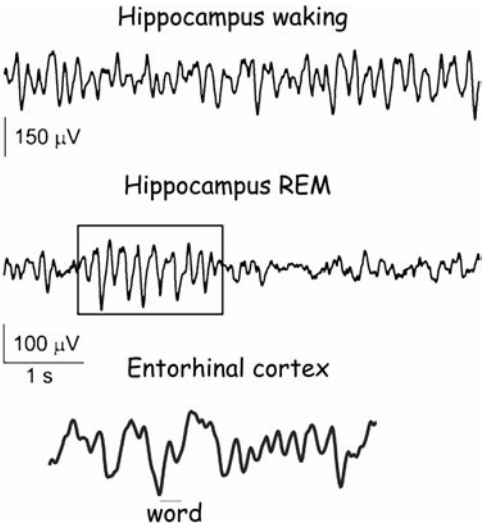

Figure 12.1. Theta oscillation in the human hippocampus–entorhinal cortex. Top: A short trace of unfiltered EEG, recorded directly from the hippocampus of a patient, during awakening shows dominance of theta frequency oscillations. During REM sleep, the same electrode exhibited short episodes of theta oscillations (Middle, boxed area). Reprinted, with permission, from Cantero et al. (2003). Bottom: Theta oscillation in the entorhinal cortex, induced by word presentation in a different patient. Trace courtesy of E. Halgren and I. Ulbert.

multisynaptic "reverberating" paths of neocortical–hippocampal loops, and the combined synaptic-conduction delays in these loops approximate the theta period. This would be an example of time-delayed, in-phase synchronization of limit-cycle oscillators. Because of the consistent and unidirectional phase offsets, unique resonant loops can be established. Under the resonant loop mechanism, the macroscopic field oscillations may not be prominent or even observable in neocortical areas. Nevertheless, the sequentially activated assemblies at each site could be identified by progressively longer phase delays to the reference hippocampal theta. The neocortical route sequences would not be active on their own and require the orchestration of the hippocampal rhythm and some external input.[4] The third possibility is that various neocortical regions are capable of generating their own local theta oscillations under the right conditions, such that hippocampal and neocortical theta oscillators entrain each other. An extension of this possibility is the stochastic resonant properties of neocortical local circuits,

4. Robert Miller was among the first to suggest that hippocampal theta oscillations may drive neocortical circuits through what he called reverberation resonance (Miller, 1989, 1991). He envisioned that the hippocampal "baseline theta oscillator" would strengthen just those cortical connections whose combined synaptic-conduction delays are the same as the theta period. Theta then can serve as the contextual retrieval signal and function as an "index" that can point to the relevant chapters of a book (Hirsh, 1974; Teyler and DiScenna, 1985).

which can extract the theta-coded message. The advantages of the second and third hypothetical mechanisms of hippocampal theta engagement of neocortical circuits are that coupling can be established by very weak links, and many cortical assemblies can be entrained with short time lags after just one cycle such that their joint outputs would be synchronized with minimal delays. As a result, distant cortical networks with nonexistent or weak anatomical connections can orchestrate their activity in such a way that their temporally locked outputs can select common downstream assemblies. Overall, these mechanisms in isolation or combination would allow top-down hippocampal–neocortical communication at a pace determined by the hippocampal theta oscillator.

Before we begin to consider specific examples, it should be clearly stated (again) that such a global treatment of oscillators is a questionable oversimplification. Descriptions of oscillators at the macroscopic level assume a single, giant harmonic oscillator and neglect the dynamics of the individual components, whose properties often crucially determine the nature of coupling or quenching. Because each network oscillator is composed of large numbers of components, the macroscopic or lumped models assume that perturbations affect each component equally and at the same time.

An early set of experiments that examined the role of theta oscillatory coupling involved the hippocampus and entorhinal cortex, the main hub between the hippocampal system and the neocortex. Ross Adey and colleagues at the University of California–Los Angeles studied the relationship between hippocampal and entorhinal theta rhythms in cats that learned a visual discrimination task in a T-maze. Early in training, hippocampal theta had a phase lead over that in the entorhinal cortex, but by the end of training the phase relationship reversed, with entorhinal theta oscillations leading the hippocampal signal. Interestingly, such phase reversals between the two structures also occurred between correct and the occasional incorrect trials in well-trained animals. On error trials, the hippocampus was leading the oscillations as in the early stages of learning. The learning-related phase shift was associated with a frequency decrease of the oscillation from 6 to 5 per second. Also, the frequency of theta oscillation was slower on error trials than on correct trials.[5] One can speculate from these early experiments that the relative phase-delayed activity of neurons in the hippocampus or entorhinal cortex determined the direction of neuronal communication between the two structures, and that the direction of impulse flow changed as a result of experience. This tentative conclusion is further supported by related studies in epileptic human patients with depth electrodes. The subjects in these experiments

5. Adey was among the first neuroscientists who benefited from NASA's space science program and, as a result, was able to use computers for the first time to process brain signals. His reports were the first to quantitatively assess cooperative mechanisms across different brain regions (Adey et al., 1960a,b). Unfortunately, the histological locations of the recording electrodes were not revealed in those reports, and there were large differences across cats. Thus, the observed phases in different cats could have arisen from implantation of the electrodes in different layers in the hippocampus and entorhinal cortex. The training-related phase leads and lags were also confounded by the parallel frequency changes.

performed a word list-learning paradigm with a free recall memory test following a distraction task. Successful as opposed to unsuccessful memory formation was associated with a general rhinal–hippocampal coherence enhancement of theta oscillations during encoding, without noticeable alterations in spectral power.[6] Studies in monkeys, carried out in Yasushi Miyashita's laboratory at the University of Tokyo, provide further support for the training-reversed direction of information. In these experiments, the time courses of perceptual and memory-retrieval signals were monitored, using single-unit recordings in the temporal and perirhinal cortex while monkeys performed a visual pair-association task. The perceptual signal reached the temporal cortex before the perirhinal cortex, confirming its forward propagation. In contrast, memory-retrieval signals appeared earlier in the perirhinal cortex, and neurons in the temporal cortex were gradually recruited to represent the sought target.[7] Coupling by theta oscillations has also been reported in the amygdalohippocampal circuit. As a result of fear conditioning, theta oscillations emerged in the amygdala of mice, with the waves in synchrony with hippocampal theta oscillations. Such temporal coordination may allow fear signals conveyed by the amygdala to be associated with the environmental context provided by spatial inputs to the hippocampus.[8]

Scalp recording of EEG in humans has provided indirect support for the role of theta oscillations in memory functions. Wolfgang Klimesch and colleagues at the University of Salzburg in Austria have been studying the role of alpha and theta oscillations in cognitive performance. They distinguish between overlapping bands of theta (6–10 cycles per second), low-frequency (6–10 cycles per second), and high-frequency (9–14 cycles per second) alpha oscillations on the basis of scalp topography and behavioral correlation. Importantly, the borders of the behaviorally defined bands vary considerably among individuals. Therefore, lumping frequency bands across subjects without determining the frequency borders in each individual can wash out important effects because these individualized bands vary independently and often in the opposite direction in different tasks. After separating the individualized alpha band, Klimesch's assessment is that sensory stimuli and semantic memory performance are best correlated with a decrease of the high alpha power ("desynchronization"), whereas increased theta power above the occipital region is associated with encoding of new information. In a typical memory task, discrete visual or auditory items appear one at a time for a few seconds each. In the recall phase, subjects are presented with some of the old items (target, e.g., robin) mixed with novel items (distractor, e.g., sparrow) and are asked to identify items that were part of the original list. The magnitude of item-induced theta power is generally larger during the retrieval than in the encoding phase. Critically, the subsequently correctly recalled items in the study

6. Coherence increases in the theta range were correlated with the memory-related changes in rhinal–hippocampal gamma phase synchronization in these same patients (Fell et al., 2001, 2003).

7. Naya et al. (2001).

8. Seidenbecher et al. (2003). For an excellent overview of the role of oscillations in amygdala function, see Paré et al. (2002).

phase are associated with a significantly larger theta power increase than incorrectly identified items, emphasizing the need for increased theta activity for successful specific encoding.[9] It is not simply a general brain state but the specific oscillatory constellation that creates favorable conditions for encoding novel information.

Although it is the theta power that covaries best with cognitive performance, alpha oscillations may also play an important role, perhaps in an indirect way, as shown by the observation that in good memory performers the baseline (prestimulus) alpha frequency is about one cycle per second higher than that of bad performers. Due to the poor spatial resolution of the scalp signal, however, the source of the recorded alpha and theta power has remained unknown. With standard recording electrodes, it is impossible to conclude whether the power increase reflects increased amplitude of theta oscillation at a single site or coherent oscillations within smaller subregions integrated by the scalp electrode.

Power increase is usually interpreted as increased synchrony, implying phase coherence of multiple sites, but this claim is hard to justify. Using high-density scalp recording and a visual working memory task,[10] Alan Gevins at the EEG Systems Laboratory in San Francisco, California, localized the enhanced theta signal to the region of the anterior cingulate cortex. Theta power increased with both enhancement of task difficulty and practice. In other working memory studies, using either verbal or visuospatial stimuli, an increase in theta coherence was observed between the prefrontal cortex and posterior association areas.[11] Although these studies connect theta oscillations to declarative and/or working memory, the relationship between neocortical and hippocampal oscillations remains unknown. Indirect support for such a connection is the observation that, in a working memory task, both encoding and retrieval items reset the MEG theta signal, whose dipole source was attributed to the anterior (uncal) hippocampus.[12]

As is the case with gamma oscillations (Cycle 10), the results obtained from scalp-recorded EEG and subdural electrode grids often mismatch. In a large clinical study, the oscillatory responses were examined at several hundred cortical and hippocampal sites in patients equipped with subdural grid and depth electrodes. The patients were presented with a short list of consonants; shortly thereafter, they were asked to report whether or not a "probe" consonant matched letters on the list. Theta activity selectively increased and was sustained throughout the trial at hippocampal sites and a portion of neocortical sites. Importantly, the increase in theta power was specific for items successfully recalled in a free

9. The many studies of Klimesch and colleagues are reviewed in Klimesch (1999, 2000). See also Bastiaansen and Hagoort (2003).

10. Working memory, also called "short-term," "immediate," "conscious," "scratch pad," or "attentional" memory is a mental workspace with limited capacity. It is very sensitive to interference. One has to continuously rehearse or "keep in mind" the items to prevent forgetting.

11. Gevins et al. (1997) and Sarnthein et al. (1998). The presence of theta rhythm in the anterior cingulate cortex in humans is directly supported by current-source density analysis of field potentials and multiple-unit activity measurements (Wang et al., 2005).

12. Tesche and Karhu (2000).

recall task. Some neocortical sites showed item-triggered phase resetting without power changes. The majority of sites with significant task-related effects were located in the occipitoparietal region, and a minority were located in the temporal region. Unexpectedly, exceptionally few sites were affected by the task in the prefrontal cortex. Although the task-related modulation of power occurred simultaneously at hippocampal and neocortical sites, the induced oscillations were rarely phase coherent. Coherence was also rare among the cortical sites, and it decreased as a power law function of distance.[13]

The simultaneous appearance of oscillations in the theta frequency without phase coherence across structures poses challenging questions regarding their functional role and origin. The least attractive explanation is that they emerge exclusively in local circuits, without any fine time-scale coordination with each other. An alternative hypothesis for the lack of sustained synchrony throughout the encoding period is that each item presented in the learning and retrieval phases produces a short-lived, unique set of coherent oscillations in a subset of the recording sites, similar to the orientation-specific gamma synchronization in varying subsets of cortical columns (Cycle 10). Under this scenario, each item activates a unique hippocampal cell assembly, which in turn produces transient coupling between the hippocampal assembly and the partnering, spatially distinct neocortical assembly. Subsequent items engage different hippocampal assemblies, each transiently coupled to specific neocortical assemblies at different sites. Experiments in rhesus monkeys support this idea. As in humans, theta oscillation in the monkey extrastriate cortex is maintained throughout the encoding period in a working memory task, and its power increases with task difficulty. However, the locally recorded single neurons respond selectively to individual visual items. The task-related enhanced firing of the neurons occurs near a specific preferred phase of each theta cycle, reminiscent of the position–phase relationship of hippocampal place cells.[14] Assuming that the successively presented items are represented by different assembly sets in the hippocampus, their outputs may engage spatially varying cortical assemblies.

Although these disparate observations in humans and monkeys are compatible with the idea that theta oscillations in the neocortex are related to those in the hippocampus, they do not provide proof. An alternative explanation is that neocortical oscillations during working memory tasks emanate from the thalamocortical networks. "Theta" in this case would reflect a slower version of thalamocortical alpha rhythms.[15] Under this hypothesis, alpha would reflect task-irrelevant activity over sites *not* participating in the computation process, which could explain why the majority of "activated" sites are confined to the posterior part of the neocortex. As reviewed in Cycle 8, alpha oscillations do not necessarily reflect

13. Kahana (2006) Kahana et al. (2001), Raghavachari et al. (2001, 2006), Rizzuto et al. (2003), and Sederberg et al. (2003).

14. Lee et al. (2005).

15. Occipital activity in the theta band may also reflect "lambda" waves, thought to be of retinal origin (Billings, 1989).

idling of cortical networks but rather indicate an active disengagement from environmental inputs with an emphasis on internal mental operations.[16] Unfortunately, without a thorough understanding of the physiological mechanisms underlying the macroscopic field patterns, one can only speculate what happens at the neuronal level.

Simultaneous recordings of hippocampal and neocortical cell assemblies in rats lend support to the idea that at least some forms of the dialogue between hippocampus and neocortex occur in the packages of theta oscillatory waves. Theta field oscillation and phase-locked discharge of multiple neurons in various cortical layers of the perirhinal and posterior cingulate cortices often occur during navigation and REM sleep. Both unit discharges and the field, when present, are phase-locked to theta oscillations in the hippocampus, although no theta dipoles have yet been reliably localized to the cortical layers. The posterior cingulate cortex has monosynaptic connections with parahippocampal and visual structures, as well as with the anterior cingulate cortex. The latter area is part of the prefrontal cortex. Areas of the prefrontal cortex are direct targets of the ventral hippocampal efferents, and a significant portion of neurons in the medial prefrontal cortex discharge coherently with the hippocampal theta rhythm. The phase-locked action potentials of the medial prefrontal neurons are delayed by approximately 50 milliseconds, indicating hippocampoprefrontal directionality.[17]

Theta phase-locked discharge of neurons in anatomically direct targets of the hippocampal system is perhaps not so surprising. But can neurons in other areas of the neocortex, several synapses away from the hippocampus, display theta phase-locking, if even transiently? Anton Sirota, a graduate student in my laboratory, addressed this question by examining the effect of hippocampal theta oscillations on the discharges of neurons in the primary somatosensory cortex. This structure was selected because it occupies a large area of the rat neocortex and because the synaptic path length is longest between the hippocampus and primary sensory areas. His first observation was that, during both navigation and REM sleep, the firing patterns of a portion of the somatosensory neurons became transiently but reliably coherent with theta oscillations while the animal was performing a navigation task or in REM sleep. Importantly, the majority of the phase-locked units were inhibitory interneurons, some of which fired rhythmic bursts at theta frequency (figure 12.2).[18] These findings at the cellular level can also explain why induced fields at various cortical sites in episodic memory tasks are not necessarily coherent with hippocampal theta oscillations.[19]

What could be the advantage of such long-range, multisynaptic entrainment? Sirota and I hypothesized that oscillatory entrainments are advantageous mainly for the entrainer, in our case, the hippocampus or, more precisely, the evolving

16. As opposed to the traditional idling role of alpha rhythms, Luria (1966) conjectured that they reflect visual imagery, internal attention, free associations, and planning.

17. Leung and Borst (1987), Collins et al. (1999), and Siapas et al. (2005).

18. Sirota et al. (2003).

19. Kahana (2006) and Sederberg et al. (2003).

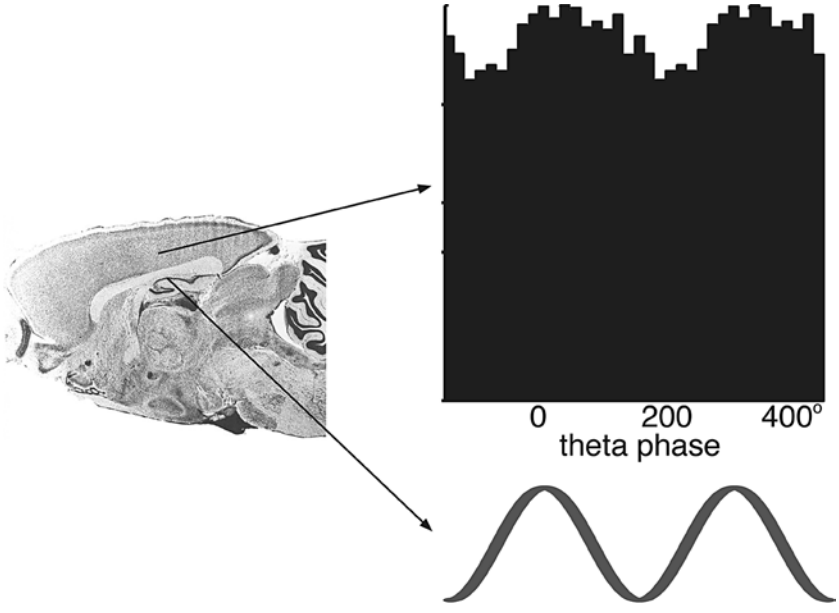

Figure 12.2. Phase-locked discharge of cortical neurons by hippocampal theta oscillations: simultaneous recording of field theta oscillation (bottom) and from a putative cortical interneuron from layer 5 of the somatosensory cortex (top histogram). Note phase-locked modulation of spike activity by the hippocampal theta cycle. Courtesy of A. Sirota and G. Buzsáki (unpublished observations).

hippocampal cell assemblies. Since the hippocampus operates in a discontiguous manner during theta oscillation, information arriving at the "wrong" phase may be ignored. However, if the hippocampal output manages to temporally bias the firing patterns of distant cortical sites by polysynaptically entraining some of their interneurons, well-timed messages from those same cortical areas will be treated preferentially over others by the hippocampus. Speaking generally, centrally organized rhythms can enhance the efficacy of their inputs by biasing them to send messages at times convenient for the oscillating receiving structure. An analogy of such directed dialogue is the boss-determined appointments with subordinates for reporting work in progress. Such a temporally specified "call-up" mechanism can be an effective solution for top-down selection of bottom-up inputs.

Hippocampal-Neocortical Dialogue during Nontheta States

The means by which large collections of neurons, within and across the vast regions of the brain, interact is not well understood. Nevertheless, it is striking that these interactions persist in all brain states but the temporal dynamics underlying

the information exchange vary from state to state. Understanding the nature of these state-dependent dialogues is of great importance because they can provide us clues about the direction and temporal windows of information transfer. These transfer processes are not continuous but packaged into compressed population events separated by renewal processes. Stating this in the framework of networks and systems, the macroscopic order parameters guide the single-cell processes at different spatial and temporal scales.

Hippocampal Oscillatory Patterns Reflect Neocortical States

Cycles 10 and 11 discussed how gamma oscillations tie together the hippocampal CA3 and CA1 regions, how the CA3 autoassociator generates an intrinsic theta rhythm, and how both theta and gamma oscillations are affected by the oscillatory patterns of the dentate gyrus. The antagonism between the activities of the dentate gyrus, the main recipient of neocortical information, and the CA3 and CA1 regions is even more prominent in the absence of theta oscillations. Behaviorally, these nontheta states involve consummatory behaviors, such as eating, drinking, and grooming and immobility, non-REM sleep, and deep stages of anesthesia.[20]

The activity of the neocortex under various anesthetics alternates between neuronal silence with nearly all neocortical principal cells sitting at a hyperpolarized level (down state) and the up state, with many neurons spiking (Cycle 7). The global shifts of activity are partially due to the toggle switching of the membrane potential in principal cells throughout the neocortex. Is this the case in the allocortex and hippocampus as well? Yoshikazu Isomura, a postdoctoral fellow in my laboratory, compared the impact of the global neocortical shifts on the activity of prefrontal, entorhinal, subicular, and hippocampal neurons. Similar to prefrontal and other neocortical neurons, both entorhinal and subicular neurons showed bimodal distribution of the membrane potential, toggling in parallel with the up-down shifts of the global neocortical activity. In contrast, hippocampal granule cells and CA3 and CA1 pyramidal neurons did not show such bimodality, adding further support to the distinct functional organization of the hippocampus. However, the hippocampus was not left unaffected by the neocortical inputs. In the dentate gyrus, gamma power increased in parallel with the up state, often with simultaneous increase of gamma power in CA3–CA1. However, when the neocortex, entorhinal cortex, and subiculum became silent, gamma power in the dentate gyrus decreased, most likely because the necessary drive from the entorhinal cortex was absent. Nevertheless, the down state in the neocortical networks was associated with gamma oscillation bursts in the CA3–CA1 system. The straightforward interpretation of these observations is that the CA3 recurrent system can generate self-sustained gamma oscillation on its own, supporting the previous contention. Furthermore, the combination of the anatomical connections and the dynamic patterns in the dentate gyrus exerts a general suppressing influence on the recurrent circuits of the CA3 system, yet at other times, the dentate can have a facilitative

20. The classical reference on behavioral correlates of hippocampal patterns in the rat is Vanderwolf (1969). For an extended review, see Vanderwolf (1988).

effect on the same target network. The mechanism of the suppression of CA1–CA3 gamma activity by the dentate gyrus remains to be investigated. A candidate mechanism is annihilation of the target oscillator by the critical intensity and phase of the dentate gamma oscillation.[21]

Oscillatory Patterns of the Hippocampus in "Offline" States

Although experiments carried out under anesthesia should be viewed with caution, the general observations discussed above are also valid in the drug-free brain. In the nonexploring rat, three basic types of patterns alternate with each other in the hippocampus: intermittent gamma oscillations, silent periods, and a unique, hippocampus-specific pattern called the sharp-wave–ripple complex. In the dentate region, gamma activity is the most conspicuous pattern. However, in contrast to the relatively uniform theta–phase-modulated gamma oscillation in the exploring animal and REM sleep, gamma oscillations are much more irregular in the absence of theta rhythm. Relatively silent periods with no cellular discharge activity alternate irregularly with short gamma oscillatory epochs, which vary substantially in both frequency and amplitude. Occasionally, just one to three waves with the period of the gamma cycle emanate from a flat baseline, with the middle wave displaying a large-amplitude, spikelike appearance. This irregular dentate gamma pattern exerts a dampening effect on the excitability of the CA3–CA1 neurons, although this process is quite complex.[22]

The third major pattern includes a "sharp wave," which is observed irregularly in the apical dendritic layer of the CA1 region as a result of a strong depolarization by the CA3 collaterals, due to the synchronous bursting of CA3 pyramidal cells. Sharp waves are the ultimate self-organized endogenous hippocampal events because they occur when the animal has no or minimal interaction with the environment. They are the first and only population pattern in the developing hippocampus. In fact, sharp waves and associated neuronal burst discharges persist when the hippocampus is completely isolated from its environment, for example, after being transplanted into a brain cavity or the anterior chamber of the eye.[23] In the intact brain, the endogenous hippocampal sharp wave emerges in the excitatory recurrent circuits of the CA3 region. The synchronously discharging CA3 pyramidal cells activate not only CA1 pyramidal cells but also interneurons and the interaction between pyramidal cells, and the various classes of inhibitory interneurons gives rise to a short-lived, fast field

21. Isomura et al. (2005). Previous findings in behaving and anesthetized animals support the competition of activity between the dentate gyrus and CA3–CA1 (Bragin et al., 1995a, 1995b; Penttonen et al., 1997). Annihilation of a trailing oscillator is described in Winfree (1980).

22. Because of their spikelike appearance, these patterns were called "dentate spikes" (Bragin et al., 1995b). The cellular-synaptic mechanisms of these spikes are identical to the gamma oscillations, and only their isolated appearance and large amplitude distinguish them from the more regular, multiwave gamma rhythm.

23. Leinekugel et al. (2002) and Buzsáki et al. (1987).

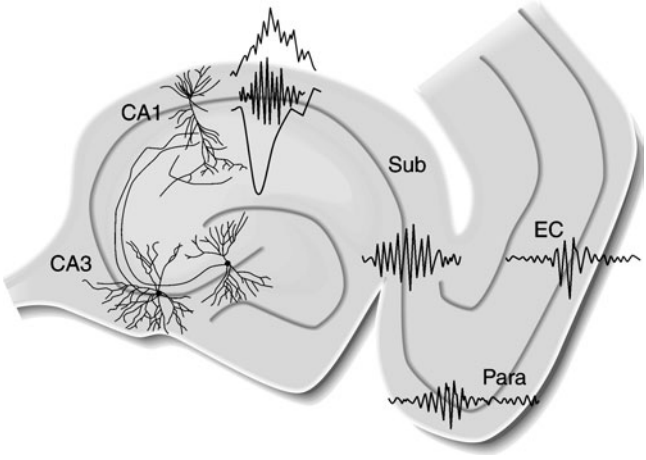

Figure 12.3. Self-organized hippocampal activity can invade large cortical areas. A synchronous population burst that emerges in the recurrent excitatory system of the hippocampal CA3 region depolarizes CA1 neurons, as reflected by a sharp wave in the apical dendritic layer, and brings about a short-lived fast oscillation ("ripple" in the cell body layer). The strong, ripple-related hippocampal activity can bring about similar population bursts in the subiculum (Sub), parasubiculum (Para), and entorhinal cortex (EC), from where it can reach widespread regions of the neocortex. The temporally "compressed," experience-dependent sequences of neurons during the sharp wave–ripple may be critical for transferring information from the hippocampus to cortex. Reprinted, with permission, from Buzsáki and Chrobak (2005).

oscillation (140–200 per second) or "ripple" confined to the CA1 pyramidal cell layer.[24]

The hippocampal sharp-wave–ripple complex has numerous remarkable features that make it a candidate pattern for consolidation of synaptic plasticity and transfer of neuronal patterns.[25] One of its major features is its widespread effect. In the approximately 100-millisecond time window of a hippocampal sharp wave, 50,000–100,000 neurons discharge together in the CA3–CA1–subicular complex–entorhinal axis of the rat, qualifying it as the most synchronous network pattern in the brain, as James Chrobak, a postdoctoral fellow in my laboratory, has described it. This number represents 5–15 percent of the local population, an order of magnitude larger than during theta oscillations (figure 12.3). This feature alone makes the sharp waves eligible for affecting neocortical targets. Its recruitment dynamics are delicately controlled by the various classes of interneurons. Both

24. O'Keefe and Nadel (1978), Buzsáki et al. (1983, 1992), and Csicsvari et al. (2000). For the potential role of axonal gap junctions between axons of pyramidal cells in the ripple event, see computational models in Traub and Bibbig (2000) and Traub et al. (2004). Sharp-wave–ripple events are present in all mammals investigated, including humans (Bragin et al., 1999). For the differential role of interneurons, see Csicsvari et al. (1999) and Klausberger et al. (2003).

25. Buzsáki et al. (1983, 2003) and Buzsáki (1986; 1989, 1996, 1998).

pyramidal and selected interneuron populations increase their spike outputs during the sharp wave, but inhibition cannot keep of with the increased excitation, resulting in a three- to fivefold gain in network excitability.[26]

The transient but substantial gain in population excitation creates favorable conditions for synaptic plasticity. However, in order for the sharp-wave–ripple events to be useful for their desired purpose, they should have an interpretable content, and the content should be modifiable. Understanding the content, of course, is a general requirement for understanding any macroscopic field pattern and requires large-scale recording of neurons. Since this strategy proved valuable for revealing the relationship between single-level behavior and theta oscillations (Cycle 12), I follow a similar line of reasoning here for sharp waves.

Modification of Self-Organized Hippocampal Patterns by Experience

In principle, neuronal activity during sharp waves can be useful in two fundamentally different ways. First, the participating neurons can discharge independently and randomly, thereby erasing or equalizing synaptic modifications brought about by specific activity in the waking brain. The expected result is a fresh *tabula rasa* of the hippocampal autoassociator, every morning ready to be filled with the excitements of the new day. This hypothetical erasure mechanism, of course, should also apply to immobility, drinking, and eating following exploratory learning, because sharp waves are present during such consummatory behaviors, as well.[27] As a result, the "noisy" or random activity during sharp waves would interfere with the synaptic modifications brought about by the preceding experience. Alternatively, the neuronal pathways used and modified in the waking brain can be repeatedly replayed during nontheta behaviors but now with the temporal dynamics of the sharp waves. This mechanism could be useful in at least three different ways. First, neuronal representations of a single episode could be replayed multiple times, assisting with the consolidation process. Second, the molecular mechanisms underlying synaptic plasticity occur in multiple stages, involving transient local synaptic modification, signaling to the nucleus, gene transcription, and eventually incorporation of a newly synthesized protein into the synapse that brought about the cascade in the first place. This complex process lasts for hours, by which time the rat undergoes at least one ultradian sleep cycle, and it is not clear how the multiple-stage molecular processes involving the cell's nucleus find their way back selectively to those specific synapses that were affected by the learning process. The selective and repeated activation of the same neurons and synapses by the sharp-wave events could be indispensable in this protracted course because the molecular traffic would still be guided by

26. The increased spike output is due to adjusting the timing of pyramidal cell discharges rather than increasing discharge rates of single cells (Chrobak and Buzsáki, 1994, 1996; Csicsvari et al., 1999, 2000).

27. Crick and Mitchison (1983) attributed such "scrambling" role to REM sleep. Recently, Colgin et al. (2004) applied this "memory erasure" role specifically to hippocampal sharp waves.

synapse-specific electrical processes.[28] The third potential service of sharp-wave bursts is the combination of various representations, that is, a nonconscious associative process. Because many more neurons are active during the sharp-wave event than in a single theta cycle or at any other comparable time window, representations that occurred at intervals longer than hundreds of milliseconds in the waking brain can be brought together into the temporal scale of synaptic plasticity. Furthermore, recently acquired information can be combined with retrieved previous knowledge, again in the critical temporal window of plasticity.[29] Finally, packaging hippocampal activity into short and synchronous bursts appears to be an especially effective way of exerting an impact on the neocortex. From this perspective, sharp waves may be the means of internally organized hippocamponeocortical transfer of neuronal information. Beneath all that turbulence, sharp waves retain and replay the information embedded in the synaptic network that gives rise to the event.

Several experiments support the above hypothetical scenario.[30] Most critically, participation of single neurons in successive sharp-wave–ripple events is not random. A small fraction of pyramidal cells participate in as many as 40 percent of successive events, whereas the majority remain silent or contribute only occasionally. Since this unequal distribution of active neurons is largely similar to the differential firing patterns of hippocampal pyramidal cells in the waking animal, an important issue is whether the firing patterns in theta and sharp waves correlate with each other. Using large-scale recordings of multiple single neurons, Matthew Wilson and Bruce McNaughton at the University of Arizona in Tucson were the first to demonstrate such a relationship. Using a well-learned behavioral task in rats, they reported that pyramidal cells with overlapping place fields preserved their pairwise temporal correlations during subsequent sleep, whereas place cells, which did not overlap spatially or temporally, rarely showed correlated firing during sleep. Several other experiments in various laboratories have confirmed the now well-accepted observation that, in an unchanging environment, the firing rates and temporal correlations of neurons are preserved in multiple sleep/wake/sleep cycles and that most of the correlated discharge occurs during sharp waves.[31] However, because in these experiments no new learning

28. Frey and Morris (1997) advanced a "synaptic tag" hypothesis for guiding this process. The activated synapse would trigger local protein synthesis and create a short-lived synaptic tag, which in turn would attract the products of gene expression, shipped globally throughout the cell. The sharp-wave replay mechanism could replace the tagging mechanism or the two processes could work in parallel to ensure input specificity of synaptic modification.

29. This combinatorial feature of hippocampal sharp wave may be responsible for the sleep-induced creativity, discussed in Cycle 8.

30. For the modification of macroscopic sleep patterns by experience and the performance enhancing effect of sleep, see discussion in Cycle 9.

31. Wilson and McNaughton (1994) and Skaggs and McNaughton (1996). Pavlides and Winson (1989) were the first to observe firing rate correlations in the waking and sleeping rat in a well-learned task. Louie and Wilson (2001) extended the waking/sleeping firing pattern observations to REM sleep, as well.

took place, one could argue that the correlation of firing rates and pairwise coactivation patterns simply reflects the stability of a hard-wired system and the intrinsically differential discharge properties of hippocampal neurons, and that sleep played no special role in the conservation of firing patterns.

One possible way to attribute a causal link to the sleep/wake correlations is to perturb the synaptic connectivity by novel experience and to detect the ensuing changes in subsequently occurring sharp waves. Zoltán Nádasdy and Hajime Hirase in my laboratory set out to pursuit this hypothesis. As expected, exposure of the animal to a novel situation, such as addition of a running wheel or novel objects to a routinely explored environment, altered the structure of cell assembly firing in both the novel situation and during the subsequent sleep cycle. The correlation between the firing rates of individual neurons in the novel environment and the subsequent sleep episode was stronger than the correlation between firing rates in the novel environment and the preceding sleep episode. The novel environment had a similar effect on coactivation of neuron pairs, as well. Neuron pairs with high wake state correlation continued to display high correlation in the subsequent sleep episode. However, some residual correlation was still present between exploration and the preceding sleep session, indicating that novelty does not entirely erase previously established relationship between neurons.

Even more direct support for the replay of learned neuronal patterns came from an analysis in which complex neuronal sequences were compared, instead of pairwise correlations. In rats, exposed to a wheel-running task for the first time, precisely timed spike sequences of multiple neurons were detected. The same neurons repeatedly fired in the same temporal order during sharp waves of sleep immediately following, but not preceding, the wheel-running experience. As expected from the dynamics of the sharp-wave events, neuronal spikes occurred at 5- to 6-millisecond intervals at the troughs of the ripple. The sharp-wave–associated sequence replay was therefore twice as fast as the cell assembly sequences compressed into a single theta period (Cycle 11), an indication of a faster search of the hippocampal autoassociator during sharp waves compared to theta oscillation.[32] Another experiment, comparing spike sequences on an elevated maze and sharp-wave–ripple complexes, found similar repetition of sequences (figure 12.4).

The simplest interpretation of these experiments is that learning in the novel environment repeatedly engaged specific sets of cell assemblies. The new temporal coalitions within members of the assemblies and across the assemblies altered the synaptic weights within the CA3 recurrent system. In turn, the newly created synaptic weights determined the spread of activity in the large synaptic space of the hippocampus. As discussed in Cycle 11, a simple rule of neuronal recruitment is that activity spreads along the path of the strongest synaptic weights. Therefore, assemblies that are activated most during the experience are held together by the strongest

32. Nádasdy et al. (1999) and Hirase et al. (2001). Lee and Wilson (2002) also showed that the neuron sequences during sharp waves were related to the sequences in the waking state. Kudrimoti et al. (1999) used an "explained variance" method and found enhanced correlation in sleep after the new experience compared to the baseline "presleep" session.

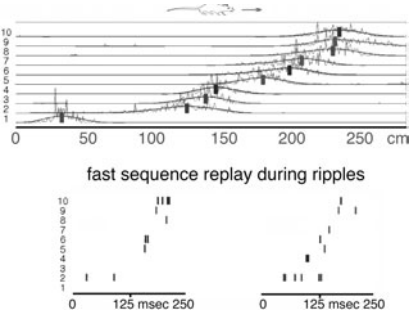

Figure 12.4. Temporally compressed replay of learned neuronal sequences. Top: Spatiotemporal firing rate changes of 10 CA1 place units on an elevated track. Bottom: Representative examples of firing patterns of the same units during two ripple events of non-REM sleep. Note the similarity between ripple-related spike sequences and the order of place-cell activation on the track. Reprinted, with permission, from Lee and Wilson (2002).

synaptic connectivity and become the "burst initiators" of the self-organized sharp-wave events, followed by the progressively less activated neurons of the learning episode. The temporal proximity of neuronal discharges during sharp waves can therefore be taken as an indication of the strengths of their synaptic connectedness. A separate experiment also showed that, by artificially changing synaptic inputs to selected neurons, their participation in subsequent sharp-wave events was altered.[33]

Transient Coupling between Neocortex and Hippocampus May Support Information Transfer

Although experiments discussed above support a "two-stage" model of memory consolidation, they do not provide direct clues about whether and how sharp-wave packaging of hippocampal assemblies can contribute to the alteration of synaptic circuits in the neocortex and, by extrapolation, to the transfer of hippocampal memories to more permanent neocortical sites. A fundamental question not addressed so far is how hippocampal sharp-wave events "know" which neurons in the neocortex were active in the waking experience, that is, which assemblies to modify offline. Given that sharp-wave–associated CA1, subicular, and entorhinal deep-layer cell assemblies can target large numbers of distributed neocortical neurons, some selection process must take place. A hypothetical solution is "tagging" those neocortical neurons that provide inputs to the hippocampus during the novel experience. In turn, the hippocampal–entorhinal output must somehow readdress the tagged neurons during sharp waves. Because during slow-wave sleep the neocortex has its own self-organized patterns (Cycle 7), the hippocampal output may often find neocortical neurons in a refractory state, unless some coordination

33. King et al. (1999) used Hebbian pairing of sharp-wave bursts and single-cell discharges to increase sharp-wave participation of neurons.

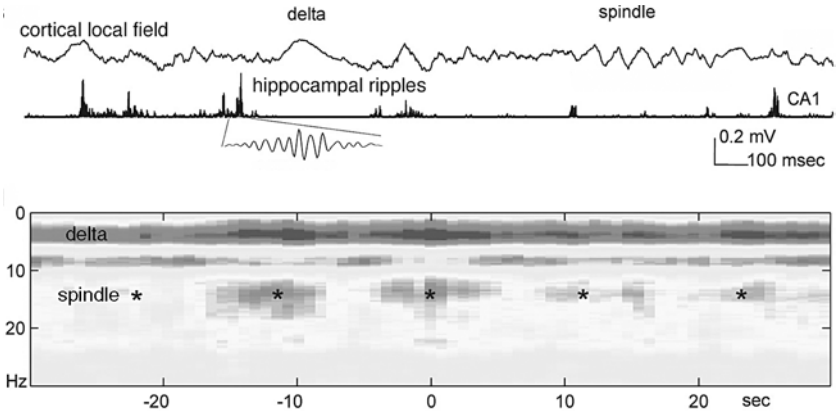

Figure 12.5. Oscillatory coupling between hippocampus and neocortex. Top: Short segment of somatosensory local field activity (layer 5) and filtered hippocampal ripples (one ripple event is shown at a fast scale below). Bottom: Averaged, hippocampal ripple-triggered neocortical spectrogram in a mouse. Note the increased correlation of power in the delta and sleep spindle (10–18 Hz) bands with hippocampal ripples. The asterisk indicates slow oscillatory (0.1 Hz) comodulation of neocortical spindle and delta waves and hippocampal ripple activity. Reprinted, with permission, from Sirota et al. (2003).

process is in place. Furthermore, sharp-wave events do not always begin with the activity of the same assembly. As in episodic memory, a cues can initiate recall at any segment of the episode. During sleep, such cues can arrive to the hippocampus from the neocortex and can select which assemblies are activated in a given sharp-wave event. Experimental findings support this hypothesis.

In general, emergence of sharp-wave–ripple complexes does not require extrahippocampal inputs. Nevertheless, when such inputs are available, the inputs may affect the time of occurrence of the ripple event and the composition of the participating neurons. As discussed in Cycle 7, the neocortical activity during down-up transitions is often amplified by the triggered thalamocortical spindles. Simultaneous monitoring of neocortical and hippocampal activity revealed that the excitability fluctuations, associated with the thalamocortical spindles, reliably affected the timing of hippocampal ripples and cell discharges, as expected from the appropriate neocortical–hippocampal synaptic delays.[34] The fine temporal structure that emerges during the co-occurrence of the relatively longer neocortical spindle and the "punctuate" hippocampal sharp wave is another example of a potentially useful "call-up" mechanism that may provide a framework for coordinated information transfer between the two structures according to the following scenario (figure 12.5). Individual sleep spindles emerge from the activity of

34. Sirota et al. (2003). Co-occurrences of ripples and sleep spindles were modulated by a 10-second slow 2 oscillation. See also Vanhatalo et al. (2004) for slow 2 oscillator modulation of excitability in the human cortex. Siapas and Wilson (1988) were the first to assume a link between sharp waves and spindles.

characteristically different thalamocortical neuronal assemblies, as evidenced by the variable spatial distribution of spindle power in successive spindle episodes. The output of the specific neocortical cell assemblies can select burst initiators of the hippocampal sharp-wave events. In turn, the biased sharp-wave–related discharge of a unique assembly of neurons in the CA3–CA1–subicular complex–entorhinal cortex axis provides a synchronous output to all their neocortical targets. Nevertheless, it will modify the synaptic inputs of only those neocortical cell assemblies that continue to spike in the spindle event. Thus, the hippocampal output message is temporally sandwiched between the cyclic discharges of spindle-activated neocortical neurons. The temporal directedness within the spindle–sharp wave–spindle sequence facilitates conditions in which unique neocortical inputs to the hippocampus and hippocampal outputs to the neocortex may be selectively modified by spike-timing–dependent plastic mechanisms. A direct proof of this hypothetical mechanism will require assembly recordings from both hippocampal and neocortical areas to demonstrate that specific assemblies in the two brain regions are brought about by a learning process and that their temporally coordinated occurrence has future behavioral consequences.

Multiplexing Representations by Multiplexed Oscillations

When multiple, transient, or sustained oscillations emerge from the same or different neuronal substrates simultaneously, how do they influence each other? Given the ubiquitous and simultaneous presence of multiple oscillators in various parts of the brain, this is a critical question. Yet, relatively little research has been devoted to the problem of cross-frequency coupling. The most frequent case is co-occurrence or comodulation of different rhythms. A trivial but robust example is the temporal correlation between cortical "up" states and gamma oscillations. A requisite of gamma oscillations is sufficient activity of cortical interneurons (Cycle 9), which is only available during the up state, while absent in the down state when all neuron types are silent. In the drug-free brain, gamma oscillations can occur in both waking and sleep states, although variance and power of the waves vary extensively across states. A particularly striking relationship is the coupling between hippocampal gamma and theta rhythms. Although gamma oscillations can be present in all states, the power of gamma activity is higher and more regular during theta-associated behaviors. Beyond the parallel covariation of theta and gamma oscillations, Anatol Bragin in my laboratory observed that the power of gamma activity varies dynamically as a function of the theta cycle. In subsequent experiments, we revealed a similar relationship in the entorhinal cortex and the neocortex, as well (figure 12.6).[35]

35. Buzsáki et al. (1983), Bragin et al. (1995), Chrobak and Buzsáki (1998), and Sirota et al. (2005). Slow rhythms often phase-modulate the power of faster oscillations. The effect can be powerful enough to trigger epileptic afterdischarges in animals predisposed to seizures (Penttonen et al., 1999).

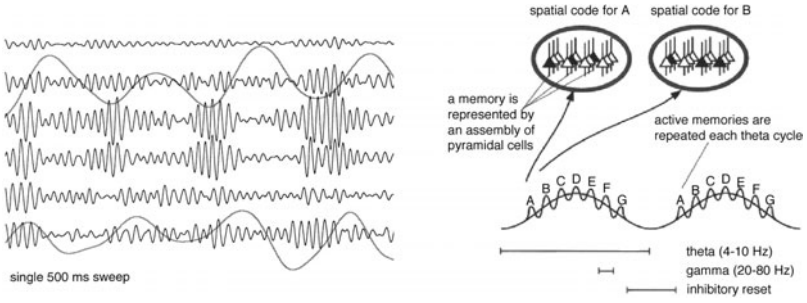

Figure 12.6. Mutiplexing by oscillatory phase modulation. Left: Simultaneous recordings from the entorhinal cortex of the rat. The slower theta and faster gamma waves were separated by filtering. Note the strong theta phase modulation of the amplitude of gamma oscillation. Reprinted, with permission, from Chrobak and Buzsáki (1998). Right: The nested gamma oscillations can be used for grouping cell assemblies. For example, repeating the assembly sequences from A to G in subsequent theta cycles can be used to hold information in working memory. Alternatively, shifting the sequences in subsequent theta cycles can serve to represent episodic memories. Reprinted, with permission, from Lisman and Idiart (1995).

Phase modulation of gamma activity by slower oscillators is potentially very important because, as discussed in Cycles 6 and 11, cell assemblies are nested within gamma waves; therefore, the slow carrier waves can serve to combine and segregate cell assemblies in successive slow cycles. Each theta wave can host between seven and nine gamma cycles. Our finding in the rat prompted John Lisman at Brandeis University in Waltham, Massachusetts, to suggest that nested gamma waves can be used to simultaneously maintain several items in working memory in humans. The theta period would define the span of memory with seven to nine items multiplexed on successive gamma cycles. Firing of neurons in each gamma cycle is assumed to be maintained by a membrane process intrinsic to each cell and established promptly at the onset of working memory. Although direct support for these assumed mechanisms is not yet available, the major innovation of Lisman's time-multiplexing model of the short-term memory buffer is that it does not require reverberating circuits.[36] Indirect support comes from experiments in human subjects demonstrating that the duration of memory scanning increases with the set size and corresponds to approximately 25 milliseconds per item "to be remembered." Thus, the number of items that can be stored by the multiplexed gamma–theta model is identical with the "magical number 7 (±2)," the psychophysically measured limit of working memory.[37] As discussed in Cycle 11,

36. Lisman and Idiart (1995) suggest that sequence information is not necessarily resident in the synaptic connections but provided by discrete oscillatory gamma cycles on a particular phase of the theta cycle. See also Jensen and Lisman (1998).

37. Packaging of items by mnemonic techniques is known as "chunking" (Miller, 1956; Sternberg, 1966).

such a multiplexing mechanism may also be responsible for providing a spatiotemporal context for episodic memories. Similarly, nested gamma activity on theta waves in the prefrontal cortex can serve as a buffer for short-term memories. Through the theta phase modulation of gamma oscillations in the prefrontal cortex, the multiplexing mechanism could provide a physiological link between short-term memory and episodic memory.

In addition to up states of sleep and hippocampal theta oscillations in the exploring rat, neocortical alpha waves in humans also modulate gamma power, and coupling of these oscillators may serve perceptual functions.[38] However, in the case of the faster alpha oscillator, the span is shorter, with a capacity limit of four or five nested cell assemblies in a single alpha wave. It is interesting to note that this value is equivalent to the psychophysical estimate of the number of objects that can be perceived at a glance, although a causal relationship between the physiological and behavioral processes has yet to be established. Further support for this postulated relationship is the classic observation that reaction time histograms show periodicities at both 25 and 100 milliseconds, corresponding to the periods of gamma and alpha oscillations, respectively. In fact, the gamma period may be a physiological measure of the upper limit of temporal resolution in the visual and somatosensory system. Stimulation of the hand and foot at the same clock time is judged perceptually as simultaneous, even though there is a temporal difference of approximately 10 to 20 milliseconds in somatosensory evoked responses, due to the longer axonal conduction delay from the foot. Because the delay is shorter than the period of the gamma cycle, the two events are perceived as simultaneous.[39]

Two or more oscillators at different frequencies can relate to each other not only through power modulation of the faster signal but also by phase-coupling of the different oscillators. Such cross-frequency phase synchrony has been observed between alpha and gamma oscillations during mental arithmetic tasks. The potential behavioral relevance of the phase-coupling mechanism is supported by experiments in humans that show a positive correlation between task load and the magnitude of phase synchrony.[40]

Further Opportunities for Oscillatory Coupling

As described in Cycle 6, there are numerous mechanisms by which oscillators of the same or different frequencies can synchronize. Whether or not a duty cycle produces synchrony (or phase-locking) of a trailing physiological event depends mainly on the strength of the functional connections and the phase dynamics of

38. Freeman et al. (2003) showed phase resetting of gamma waves at alpha rates.

39. VanRullen and Koch (2003) is an excellent review of both old psychophysical experiments and the relevant brain rhythms that may underlie the periodicities of reaction times and subjective judgment.

40. JM Palva et al. (2005); S Palva et al. (2005).

the trailing oscillator. Randomly occurring inputs cannot synchronize oscillating targets. On the other hand, inputs with various phase dynamics can have predictable effects on a target oscillator. Two oscillators with nearly equal frequencies can communicate with each other in the sense that the phase (timing) of one of them becomes sensitive to the phase of the other. We have discussed simple cases, such as one-to-one coupling between mutually connected gamma oscillators. We also illustrated the consequences of minimal frequency differences, which can give rise to systematic phase precession or phase retardation. Because each perturbation exerts a lasting effect on the oscillator, subsequent effects are typically cumulative, producing a systematic forcing effect. Another simple case is one-to-two locking, or frequency doubling. In fact, frequency locking can occur between any two or more oscillators with an integer period relationship. In principle, virtually infinite numbers of combinations are possible but the limited number of classes of oscillators that can be simultaneously present in the same neuronal substrate puts severe constraints on the possible numbers of combinations.[41] Some arrangements enhance, whereas others annihilate each other.[42] To date, very few rhythm combinations in the brain have been studied or understood. Among them, "desynchronization" is a well-studied but little-understood phenomenon. The term typically refers to the quantitative reduction of alpha activity in the scalp-recorded signal upon presentation of a stimulus. However, the stimulus often induces or enhances gamma frequency oscillations, which may be the cause of the reduced alpha power. The best, albeit artificial, demonstration of annihilation of a slow rhythm by a high-frequency oscillation is the reduction of Parkinson tremor by constant high-frequency stimulation of the subthalamic nucleus.[43]

Coupling of oscillators having similar frequency but arising from different architectures, such as the hippocampus and neocortex, provides special challenges because even identical perturbations of similar macroscopic oscillators, which emanate from different physical substrates, can result in different outcomes. Coupling oscillators of two or more frequencies can generate complex envelopes of population activity and synchrony. Because such compound envelope oscillators can generate high-dimensional patterns, they can be very useful for encoding information.[44]

41. Combinations of oscillatory coupling are also limited in music. It has been claimed repeatedly that music is a matter of numbers. J.S. Bach used formal mathematical patterns in his organ fugues, e.g., the Fibonacci succession (1, 1, 2, 3, 5, 8, . . . , in which each number in the succession is the sum of the two previous ones). Béla Bartók also believed that there is a numerical logic that is pleasing to the ear (Lendvai, 1971).

42. Tass (1999) is a mathematically detailed treatment of phase-locking of oscillators.

43. For a review of possible mechanisms of deep brain stimulation, see Garcia et al. (2005). Better understanding of oscillators will lead to more rational stimulating regimes and more effective therapies.

44. Friston (2000) calls interregional coupling between different frequencies "asynchronous." His main argument for its importance is the nonlinear nature of coupling between different bands, as opposed to "simple," linear pairing within the same frequency band. See also Bressler and Kelso (2001).

A major motivation for studying the mechanisms of oscillatory coupling is to use such understanding for describing the direction and strength of functional connectivity between brain areas of interest. Unfortunately, there is no general mathematical or computational theory of oscillatory networks of multiple interacting oscillators. In the absence of such a theory, prediction of functional or effective connectivity on the basis of field measurements alone remains a conjecture. All known models are likely special and perhaps simplest cases of all possibilities. Nevertheless, regardless of the mechanisms, oscillators tend to synchronize transiently or for extended periods and thereby influence neuronal activities. It is therefore perhaps not outrageous to state that a requisite for understanding network and system interactions in the brain is an understanding the nature of oscillatory coupling.

Briefly . . .

Top-down and bottom-up processing of signals is a mere abstraction. In brain networks, there is no "top," since activity at any level can be transmitted to other levels, ascending or descending. The termination of a particular computation is heralded by time, marked typically by inhibition of activity, rather than by some defined anatomical boundary. Oscillatory packaging of information can define the length of the messages, and this same mechanism allows for efficient exchange of information across anatomical domains. Messages between areas can be exchanged by forced oscillations, resonant loops, or transient oscillatory coupling. Human scalp, depth, and subdural recording studies consistently describe increased power of theta oscillations in memory tasks. Increased power in the theta band during the practice ("encoding") phase is specific to items retrieved successfully. However, instances of increased theta power observed at several cortical sites are rarely coherent with each other or with the simultaneous increase of theta power in the hippocampus. A possible interpretation for the lack of sustained synchrony between the hippocampus and neocortical sites is that each item presented in the learning and retrieval phases engages varying subsets of typographically distinct, short-lived oscillations in unique neocortical sites. In support of this hypothesis, neocortical neurons various allo- and neocortical regions are phase-locked transiently to hippocampal oscillations in rodents. The advantage of such a long-range, transient entrainment of cortical assemblies to hippocampal theta is that assembly messages can reach the hippocampus at times (phases) when its receiving state (i.e., sensitivity for perturbation) is most optimal. This temporally specified "call-up" mechanism is a particularly effective solution for input selection.

Exchange of information between the hippocampus and neocortex continues during times when the brain is disengaged from the environment ("offline" states), although at a different temporal scale. The hippocampus, even in the absence of neocortical inputs, can give rise to self-organized patterns. The most

synchronous population activity arises from the CA3 recurrent collateral system that brings about short-lived fast oscillations in the target CA1–subiculum–parasubiculum–entorhinal cortex output circuits, known as the sharp-wave–ripple complex. Part of the content of these oscillations reflects activity of neurons activated in the preceding waking periods. Through the temporal compression mechanisms of sharp waves, recently acquired information can be combined with retrieved previous knowledge in the critical temporal window of plasticity. The neuronal content of individual hippocampal sharp waves may be biased by thalamocortical spindles. Because individual sleep spindles may emerge from the activity of unique thalamocortical neuronal assemblies, the synchronous hippocampal output can selectively target the actively discharging neocortical neurons because the compressed hippocampal message is temporally sandwiched between the cyclic discharges of spindle-activated neocortical neurons.

The ubiquitous and simultaneous presence of multiple oscillators in various parts of the brain often leads to transient cross-frequency coupling or phase-modulation of the power of a faster event by a slower oscillator. Two such well-studied coupling mechanisms are the gamma power modulation by theta or alpha oscillations. The transiently and consistently emerging nested gamma cycles may serve as multiplexing mechanisms for sustaining working memory content or perceptual functions. Although transient coupling of various oscillators is little studied, these compound envelope oscillators may be particularly useful for encoding neuronal messages because they can generate high-dimensional patterns. Unfortunately, the story stops here for now, just as it begins to get really interesting, because the mechanisms of coupling of multiple oscillations are poorly understood.

Cycle 13

Tough Problems

> Knowledge is not a series of self-consistent theories that converges toward an ideal view; it is rather an ever increasing ocean of mutually incompatible (and perhaps even incommensurable) alternatives, each single theory, each fairy tale, each myth that is part of the collection forcing the others into greater articulation and all of them contributing, via this process of competition, to the development of our consciousness.
>
> —Paul Feyerabend

The sleek, 59-story Citicorp Center, one of the most daring engineering designs in New York City's history, is set on four massive columns, positioned at the center of each side, rather than at the corners. This design allowed the northwest corner of the building to cantilever over St. Peter's Lutheran Church. But slenderness and beauty of buildings always come with a cost. Skyscrapers tend to sway in high winds and in the seismic waves generated by earthquakes, causing them to oscillate in various ways depending on the direction of wind force or ground motion. Such oscillations can be destructive to the buildings or simply unpleasant for the people working in them. Since it is virtually impossible to construct buildings without resonant features, it is easier to build light structures capable of oscillations and to provide adequate damping. To compensate for the unwanted effects, William LeMessurier, the chief structural engineer of the Citicorp Center, designed a device known as the "tuned mass damper" to moderate the tower's sway. It consists of a 400-ton concrete block that can slide in a steel pan filled with oil, placed on the top of the building. The counterbalanced movement of the damper effectively annihilates the unwanted oscillations of the building.[1]

1. Taipei 101 in the capital of Taiwan, currently the tallest building in the world, has a 730-ton tuned mass damper suspended between the 88th and 92nd floors, stabilizing the tower against earthquakes, typhoons, and wind. The damper reduces up to 40 percent of the tower's movements. See http://www.popularmechanics.com/science/technology_watch/1612252.html.

Tall buildings, bridges, and many other artifacts possess oscillatory and resonant properties that rarely serve a purpose, and most often these properties are outright detrimental to function. These everyday examples automatically pose a thorny question: are oscillations an essential ingredient of the brain "design," or are they simply an inevitable byproduct of the opposing forces that are so ubiquitous in neurons and neuronal networks? Throughout this volume, I have tried to convince the reader that oscillations in the brain serve useful functions and that, without understanding these rhythms, the brain cannot be fully understood. However, I postponed addressing the difficulty involved in providing a definite answer to this difficult question. I also claimed that evolution took advantage of the ease with which synchrony can be brought about by oscillations at multiple temporal and spatial scales. However, I have not addressed the tough question of whether oscillations are critical for the emergence of the most complex brain operations, as well. Because oscillations and complex systems have been extensively discussed in the consciousness debate, it would be unfair to finish a book on brain rhythms without bringing up this much-debated issue.[2] Below are my thoughts, without pretending that I have the right solutions to these difficult problems.

Brain without Oscillations?

Most experiments discussed in the preceding Cycles dealt with correlations between some overt or covert behavior and oscillations. Providing only correlations, as supportive evidence for a function, is usually viewed with skepticism. In general, there are two types of objections presented against the case for brain oscillations. First, "I do not see them in my experiments; therefore, they do not exist or are not essential." Second, "My intervention eliminated the oscillations but did not affect behavior." These objections are relatively easy to dismiss on logical grounds. For example, the absence of evidence (not seeing it) is not sufficient evidence against the existence of a rhythm. One should look harder and use higher resolution methods. Furthermore, elimination of the rhythm may not have been complete, or the behavior under investigation may not have depended on the network examined. Arguments in favor of rhythms are similar and equally vulnerable. First, "In my experiments, a specific behavior is always accompanied by a

2. Crick and Koch (1990) suggested gamma oscillation as a carrier of conscious experience, although they subsequently rejected it in favor of a special type or group of neurons with hitherto undisclosed features (Crick and Koch, 2003; Koch, 2004). More recently, they pointed to the claustrum as the critical structure in consciousness because of its widespread cortical and subcortical connections (Crick and Koch, 2005). Rodolfo Llinás conjectured that consciousness is the product of a resonance between the specific and nonspecific thalamocortical systems in the gamma frequency range (Llinás et al., 1994). Freeman (1999) describes consciousness as a two-step process, led by the intentional causation self and followed by the awareness of the self and its actions. The two steps are realized through hierarchically stratified kinds of neural activity, but the functions and nature of neuronal activity of these processes are not detailed.

particular oscillation." Second, "Whenever my intervention affects oscillations, behavior is always impaired." These arguments can also be easily dismissed. First, correlation is not causation. Second, the intervention may not have been selective enough, and the behavioral impairment may not have been caused by the absence of oscillations but by some unwanted and unobserved side effect of the perturbation.[3]

The acid test for providing a definite proof for the essential role of brain rhythms in computation and brain function would be to selectively eliminate them and examine what is left after the complete lack of oscillatory timing. Unfortunately, this test in its pure form cannot be performed for reasons I discussed in previous Cycles. I briefly reiterate those arguments here. Most oscillations in the brain are not driven by an independent pacemaker but emerge from nonoscillatory constituents. Even when a pacemaker is identified, it is typically embedded in large networks with a complex feedback to the rhythm-generating neurons. As a result, oscillations are not a product of some independent function or structure that can be physically removed or selectively manipulated, leaving the rest of the brain patterns invariant. In fact, there is a logical absurdity in the quest of expunging oscillations selectively. Oscillation is an emergent property; that is, it reflects an order parameter that, in turn, affects the parts that gave rise to it. Thus, there is nothing "extra" to eliminate without fundamentally interfering with the elementary properties of the parts. Oscillations and other emerging collective patterns do not have "receptors" that can be affected by drugs or other means; only individual neurons do. It is not possible to selectively eliminate a rhythm without altering membrane channels, synapses, firing patterns of individual neurons, or their temporal interactions.[4] The problem in the quest for selective elimination of an order parameter lies in the reciprocal causal relationship between parts and the whole of an emergent quality, such as an oscillation.

Given the difficulty in providing an acid test, the baffling question naturally arises of whether a brain without oscillations can function properly. In principle, the answer is yes, as long as synchrony of neuronal assemblies can be brought about by some other mechanism(s) at the right time scales. In other words, what may not be essential is the rhythmic aspect of synchrony. As discussed in Cycle 5,

3. A scientific hypothesis or theory, of course, cannot be proven. A proof can be provided only when the rules are known, as is the case in mathematics. But in science, the rules are not known. Hypotheses and theories are constructed to guess what those rules might be. Good theories are not proven but rather are not (yet) replaced by more universal theories.

4. Nearly all interventions that affect oscillations are associated with gross changes of firing rates and/or alteration of the balance between excitation and inhibition. Our laboratory found a notable exception to this general rule. Activation of cannabinoid receptors, the brain targets of marijuana, preserved the firing rates of both pyramidal cells and interneurons in the hippocampus. Nevertheless, it reduced or eliminated theta, gamma, and ripple oscillations. The effect is due to a balanced reduction of presynaptic release of both GABA and glutamate and the ensuing reduction of population synchrony. While individual neurons keep emitting the same numbers of action potentials under the drug's influence, the spikes are no longer associated with assembly behavior (Robbe et al., 2005). The impairment of oscillation and synchrony may explain the detrimental memory effects of marijuana.

computers, TV sets, and other devices can also run, in principle, without oscillatory clocks, provided that some other mechanisms do the necessary temporal coordination across all levels of computation. If proper timing can somehow be provided by a nonrhythmic solution, the same brain hardware could perform all functions. However, this imaginary brain has to deal with further problems. First, it has to eliminate or randomize all time constants of its constituent neurons and their connections, because such constants are natural sources of oscillations. Second, it should eliminate the balance between opposing forces, such as excitation and inhibition or ion influx and outflux, because these opposing forces are also natural forces of oscillations. Alternatively, special mechanisms should be introduced for the annihilation of the emergent oscillations. Elimination of oscillations would also require introducing other mechanisms to keep track of time. In other words, avoiding oscillations and their consequences on the population behavior of neurons is much more complicated than exploiting the synchronization consequences of naturally emerging oscillations. Oscillations are ubiquitous in all brains, small and large; therefore, it is expected that such inherent features would be exploited by evolution. Rhythms naturally arise from the opposing forces that are so fundamental for brain operations, and oscillations are a "free" source of synchronization and timing. Understanding the utility of brain rhythms is possible only from this evolutionary perspective. On the other hand, the evolutionary argument also implies that oscillations play a role at all levels of brain function, from the simplest to the most complex, including the subjective character of brain computation.

Consciousness: A Function without Definition

What is the difference between a blink and a wink? The straightforward answer is that you must be conscious to execute a wink whereas blinking is a simple reflex. And what is the difference between declarative and nondeclarative memories? The answer is that we are aware of declarative memories; therefore, we can consciously declare them, which is not the case for nondeclarative memories. The explanatory power of these answers, of course, depends on the understanding of the hypernym "consciousness," which supposedly makes the distinction between the declarative and nondeclarative or voluntary and automatic clear. Consciousness is the crutch of cognitive neuroscience, perhaps the most widely used covert explanatory tool for the classification of mental phenomena. Yet, this frequently used hypernym does not even have a definition. Is it a product, a process, or a thing? There is not even good agreement what the theory about consciousness would be like.[5]

5. Stating that a wink is voluntary whereas the blink is involuntary faces the same linguistic problem since the hypernym "volition" remains undefined. Juarrero (2000) is a good guide for the philosophical debate about the voluntary vs. involuntary distinction. The compilation of essays on the self

Although definitions of consciousness vary, from those proposed by philosophers to those put forth by practicing anesthesiologists and neuroscientists, it may be helpful to list some of the suggested definitions. The reductionist's view is amply exemplified by Carl Sagan's famous statement: "My fundamental premise about the brain is that its workings—what we sometimes call the 'mind'—are a consequence of its anatomy and physiology and nothing more."[6] In essence, this and similar statements claim that conscious behavior is the direct product of brain activity. However, they fall short of explaining the "hard" question of why we are aware of some brain operations but not of others, or, in other words, why some neural representations are translated into mental representations whereas others are not.[7] Sagan's reductionistic definition also misses the fact that the brain is embedded in a body and an environment, and it is questionable whether a single brain in isolation would be conscious.[8] The neuroscientist E. Roy John defines consciousness as

> a process in which information about multiple individual modalities of sensation and perception is combined into a unified multidimensional representation of the state of the system and its environment, and integrated with information about memories and the needs of the organism, generating emotional reactions and programs of behavior to adjust the organism to its environment.[9]

This contextual definition has the advantage of not being exclusive, and it can incorporate issues such as whether some animals have a conscious experience similar to that of humans. Giulio Tononi at the University of Wisconsin in Madison defines the problem within the context of information theory: the brain's capacity to integrate and differentiate information corresponds to the quantity of consciousness.[10] In contrast to these nominal definitions stands the Cartesian dualistic view that consciousness is a thing, independent of the brain or other matter.

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and soul by Hofstadter and Dennett (1981) is a nice summary of ideas about consciousness and the mind. Christof Koch's success book (Koch, 2004) discusses the numerous issues involved in defining the problem.

6. Sagan (1977), p. 26.

7. The "hard" problem of consciousness is how feelings arise. All other issues are considered "easy" or manageable because they can be understood by neural mechanisms (Chalmers, 1996).

8. In common parlance, consciousness denotes being awake and responsive to one's surroundings. The word "consciousness" comes from the Latin *con* (with) and *scio* (to know), meaning "that with which we know." However, in many languages it means "shared knowledge," referring to a "calibration" of a brain's output in light of responses by others to those outputs (Szirmai and Kamondi, 2006). Plum and Posner (1980) define consciousness as "the state of awareness of self and the environment." (p. 242). This medical definition only shifts the problem to another unexplained hypernym, "awareness." Faced with the difficulty of an objective definition, the usual attitude is to take the meaning of consciousness for granted ("Man, if you gotta ask what jazz is, you will never know"—Louis Armstrong) or ignore it ("If you can't explain it, deny it").

9. John (2005), p. 145.

10. Tononi's information theory model of consciousness (Tononi, 2004) implies that subjective experience is one and the same thing as a system's capacity to integrate and differentiate information.

Faced with the difficulty of providing an objective definition, an alternative approach is to ask what brain systems are involved in those behaviors that are usually characterized as signifying consciousness and what distinguishes them from systems that do not support consciousness. For example, instead of distinguishing between declarative and nondeclarative memories, we can classify experience as whether or not it depends critically on operations of particular brain structures (e.g., hippocampus-dependent memory). Below, I follow this approach and suggest that brain systems that give rise to the subjective conscious experience require special anatomical connectivity and a special constellation of oscillations that characterize the mammalian cerebral cortex. My goal is not to take sides in the consciousness debate but to contrast architectures of different evolutionary lineages and their performance constraints and convince the reader of the viability of this approach.

Networks That Do Not Feel

I have discussed two distinct anatomical "design" principles so far, each of which serves different functional roles. The relatively random connectivity of the hippocampus is ideally suited for storing and recalling arbitrary events embedded in a spatiotemporal context. The scalable, small-world-like architecture of the neocortex, on the other hand, can effectively deal with the statistical regularities of the environment, can combine or bind the various features, and can make calculated decisions on the basis of complex features, such as previous experience and the current state of the network upon which the environmental inputs impinge. There is general agreement that the neocortex is essential for awareness and that the hippocampus-supported episodic memories give rise to the "feeling of individuality." The essence of cortical operation is that, whatever computation takes place locally, other parts of the cortex get informed about it, due to the intermediate- and long-range connections and oscillatory coupling mechanisms. Conversely, self-organized (spontaneous) activity in large cortical areas perpetually influences the nature of local processing of external inputs. In other words, computation in the cerebral cortex is global.

The implication of his theory is that any physical system that is capable of integrating information, irrespective of what it is made of, must have subjective experience. Subjective experience, as integration, is graded, not all or none. The brain's capacity to integrate information grows with increasing brain size; therefore, larger brains, in general, are "more conscious." The medical definition of brain death indirectly supports this "information integration" model of consciousness: the total and irreversible loss of the brain's capacity to integrate and coordinate the functions of the body—physical and mental—into a functional unit. A tacit assumption of the information integration model is that information is a physical reality, independent of the observer, and the observer's brain only manipulates or transforms the objective reality. However, as discussed in Cycles 9 and 12, representation of the outside world is a combination of some ego-filtered input and past experience. Thus, the paradox is that consciousness of the brain is explained with a measure that is the product of the brain itself.

Because a major claim of this book is that the complex wiring of the neocortex supports its complex ($1/f$) self-organized network patterns, it is instructive to look at other structures that followed different evolutionary paths and that do not support $1/f$ type self-organization. Two such prime examples are the cerebellum and the basal ganglia.[11] Another reason for comparing these structures with the organization of the neocortex is that even complete damage of the cerebellum or basal ganglia does not abolish consciousness.

Circuit Plan of the Cerebellum

The cerebellum, or "little brain," has approximately the same number of cells as the rest of the brain combined, yet it occupies less than 10 percent of the human skull volume. The reason for such an efficient space savings is that the cerebellum is a truly locally organized structure. It receives its main inputs from the cerebral cortex, the basal ganglia, the reticular system, and spinal pathways containing sensory inputs from muscles spindles, tendons, and joints. Through these inputs, the cerebellum continually monitors the activity of skeletal muscles and informs brain areas that regulate these muscles. The result is the execution of rapid, skilled movements at speeds that are much faster than can be controlled by the "conscious" sensory systems.[12] These computations are carried out in the anterior and posterior lobes, whereas the more ancient flocculonodular lobe is concerned primarily with vestibular functions, such as posture and eye movements. The surface of the cerebellar cortex is increased by shallow fissures, which create multiple folia. However, there is no corpus callosum or intermediate- or long-range associational paths, nor there are other space-expensive connections. Furthermore, there are no substantial regional variations that would justify cytoarchitectural classification, similar to the Brodmann areas of the neocortex. Unlike the cerebral cortex, the cerebellum is not a mammalian invention. All vertebrate animals have a cerebellum with highly preserved phylogenetic homology, and it continues to serve identical functions.[13]

Computation in the cerebellar cortex is carried out cooperatively by four types of GABAergic inhibitory cells—the Purkinje cells, basket cells, stellate cells, and Golgi cells—and excitatory granule cells (figure 13.1). Purkinje cells are the principal computational neurons of the cerebellum and exhibit many differences from the pyramidal cells of the cerebrum. There are 15 million Purkinje cells in the

11. Paul MacLean's reptilian archipallium (olfactory bulb, brainstem, mesencephalon, cerebellum, and the basal ganglia; MacLean, 1990) is characterized by lack of intelligence and subjectivity and no sense of time and space.

12. A point in case is Glenn Gould's legendary speed of finger movements in his 1955 recording of Bach's Goldberg Variations. It almost seems impossible that fingers could move that fast with such perfectly calculated temporal precision! Motor practice can likely "chunk" long passages of movement sequences into a "ballistic-type" action without a need for detailed sensory feedback.

13. A short review of the evolution of the cerebellum is Bell (2002). For a thorough exposure to the cerebellum, consult the classic reference Eccles et al. (1967). Although neocerebellar circuits receiving and targeting nonmotor neocerebellar areas may support nonmotor functions, as well, the nature of computation in these circuits likely remains the same.

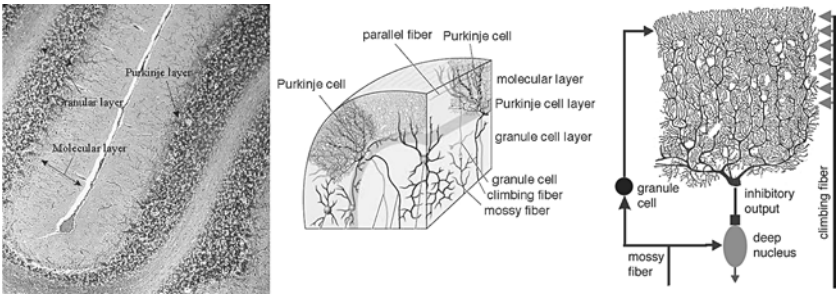

Figure 13.1. The cerebellum is organized as multiple parallel loops without interloop communication. Left: Histological section through a cerebellar folium. Middle: Position of cerebellar cell types. Purkinje cells are juxtaposed to each other with little overlap of their large dendritic trees. Right: Inhibitory loops complement the mossy fiber–deep cerebellar excitatory loop. The short loop involves the climbing fiber–Purkinje cell–deep nucleus feedforward path, whereas the long loop includes the mossy fiber–granule cell–Purkinje cell–deep nucleus path.

human cerebellum. The extensive dendritic arborization of the Purkinje cell is the most elaborate in the brain. However, in contrast to the cortical pyramidal cells that have cylindrical dendritic arbors and extensive mutual overlap with thousands of other nearby pyramidal cells, Purkinje cells are flat, and their dendrites hardly touch each other. This organization provides maximum autonomy for each Purkinje cell.

The principal source of glutamatergic excitation in the cerebellar cortex comes from the small but numerous granule cells, densely packed below the cell bodies of Purkinje cells. There are more granule cells (~10^{11}) than all neurons combined in the neocortex. However, they have very small dendrites and receive inputs from only three to five so-called mossy fibers, which originate mainly in the brainstem. The remaining three sets of neurons are present in smaller numbers. Basket cells innervate the somata of Purkinje cells, whereas stellate cells inhibit the dendrites. The fifth cell type, the Golgi cell, inhibits granule cells.

The basic cerebellar circuit can be conceived as three sets of loops attached to the rest of the brain (figure 13.1, right). The short loop involves the mossy fibers from the brainstem area, which innervate the deep cerebellar nuclei.[14] The outputs

14. Three nuclei compose the deep cerebellar complex: the dentate nucleus, the interposed nuclei (which is composed of the emboliform and globose nuclei), and the fastigial nucleus. They act as "relays" for information in and out of the cerebellum and receive topographically arranged inputs from regions of the cerebellar cortex. The fastigial nucleus controls trunk movements and receives inputs from the midline, also called the vermis for its wormlike appearance. The interposed nuclei are innervated by the intermediate zones or paravermis and control ipsilateral limb movements. The main input to the dentate nucleus is from the larger lateral hemispheres. This complex is thought to be involved in motor "planning," i.e., prediction and coordination.

from these nuclei affect structures primarily involved in motor control. The two longer loops involve the cerebellar cortex and are more elaborate. In addition to the deep cerebellar nuclei, collaterals of the mossy fibers address thousands of granule cells. The granule cells then project axons into the outer molecular layer of the cerebellar cortex, containing the dendrites of Purkinje cells. Here, the axons bifurcate and form fiber bundles, which run parallel to the cortical surface and perpendicular to the flat dendritic trees of the Purkinje cells. The very thin, unmyelinated parallel fibers each pass through 500 Purkinje cells, and each Purkinje cell receives information from an estimated 200,000 parallel fibers. The goal of this arrangement is to disperse or sparsify the inputs into a large synaptic space for refined computation. In turn, the synchronous discharge of a very large number of convergent granule cells is needed to bring their target Purkinje cell to threshold, whose output spiking activity inhibits neurons in the deep cerebellar nuclei. This mossy fiber–granule cell–Purkinje cell loop is therefore a feedforward inhibitory path superimposed on the short loop.

The other feedforward inhibitory loop is a "shortcut" that originates in the inferior olive of the brainstem, bypasses the granule cells, and terminates directly on the Purkinje cells.[15] Each of these so-called climbing fibers innervates a single Purkinje cell but with multiple contacts, so that their spiking activity can induce burst firing in the Purkinje cell. In short, the canonical circuit of the cerebellar cortex is two parallel feedforward inhibitory loops that exert differential and elaborate control over the output deep cerebellar neurons.[16] This anatomical arrangement suggests that cerebellar "modules," which roughly correspond to the extent of parallel fibers, process the incoming inputs locally, but they do not need to consult or inform the rest of the cerebellum about the locally derived computation.

Circuit Plan of the Basal Ganglia

Another major loop attached to the brainstem–thalamocortical system involves the basal ganglia. Similar to the cerebellar loop, the cortex–basal ganglia–thalamocortical pathways have major inhibitory steps in the loop (figure 13.2). The projections from one step to the next are largely topographic, providing two

15. The inferior olive or inferior olivary nucleus is a homogeneous collection of gap junction-connected neurons in the medulla oblongata lateral to the pyramidal tract. Its axons form the climbing fibers that terminate on cerebellar Purkinje cells. The nucleus is often thought of as a pacemaker because its neurons individually and collectively oscillate at 4 to 10 hertz (Llinás and Yarom, 1981; Bal and McCormick, 1997).

16. For functions and dysfunctions of the cerebellum, the best summary remains Eccles et al. (1967). Motor learning is typically studied by classical conditioning. The conditioned stimulus is carried by the thin, slow-conducting mossy fibers, whereas unconditioned stimulus is represented by the climbing fiber input. By proper timing of these inputs, the efficacy of parallel fibers on their target Purkinje cells can be effectively modified (Ito, 1989; McCormick and Thompson, 1984; Thompson 2005). *In vivo* recordings from single granule cells show that mossy fiber excitation is essential for their spiking activity (Chadderton et al., 2004).

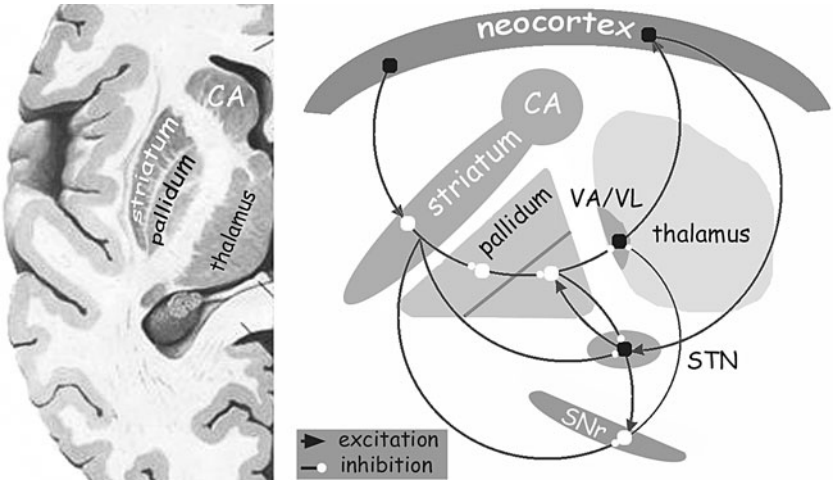

Figure 13.2. Inhibitory loops of the basal ganglia. Left: Location of the major structures of the basal ganglia in a horizontal section of the human brain, including the striatum (caudate nucleus, CA, and putamen and pallidum). Right: Major connections of the basal ganglia. The multiple inhibitory loops are funneled onto the relatively small ventralis anterior and ventralis lateralis (VA/VL) nuclei of the thalamus, affecting cortical–thalamic–cortical communication. The multiple loops include neocortex–striatum–pallidum; neocortex–striatum–substantia nigra pars reticulata (SNr), neocortex–subthalamic nucleus (STN)–pallidum; and neocortex–STN–SNr.

possible scenarios for computation. The first possibility is a reentrant loop. For example, the supplementary motor area 1 and the frontal eye-field representation in the primate motor cortex send inputs to the basal ganglia and thalamus, and the pathways remain segregated all the way before returning to the cortical cell groups where they originated. The second possibility is that the activity "spirals" in the loop so that the return message will address areas different from its origin. In both cases, there is little integration between the participants of the separate loops, another case for parallel processing. Parallel processing does not require recurrent excitatory or long-range circuits but comes with the caveat that no global computation can take place because information is shared only by adjacent local circuits.

The collective term "basal ganglia" refers to the serially connected striatum, globus pallidus external segment, and globus pallidus internal segment (entopeduncular nucleus in rodents)/substantia nigra pars reticulata. What makes these large gray masses so special is that nearly all of their neurons use GABA as a neurotransmitter. Besides the cortex, a major glutamatergic excitatory input with reciprocal connections to pallidum and substantia nigra is the subthalamic nucleus, a hub with numerous other connections. In addition, the midline and intralaminar thalamic nuclei provide further excitation. Finally, the ventral thalamic nuclei provide the cerebellum a link to the basal ganglia.

The striatum receives its major excitatory inputs from the neocortex and allocortex. More than 95 percent of its neurons are of the same kind, called medium spiny neurons, which receive cortical inputs on the spines and thalamic inputs onto their dendrites and spines. The axons of these principal neurons arborize locally, covering a disk with a diameter of a several hundred micrometers before giving rise to the projection axon, which reaches target cells in the external pallidum or substantia nigra. These projection cells are complemented by two groups of cells, another inhibitory basket cell-like interneuron and a large cholinergic neuron, which are reciprocally connected to the principal cell type. These three major cell types compose the computational circuit of the striatum. Interactions are limited by the extent of the local collaterals, and there are no options for long-distance talk without the assistance of other structures. Given the similarity of cytoarchitecture and computation throughout the striatum, the differential behavioral effects in the different parts must come from the specificity of their inputs.

The cell organization in the target external pallidum is similar, except that the principal cell type here has sparsely branching but very long, smooth dendrites. The neurons, like Purkinje cells, are flat. There is an order of magnitude fewer pallidal cells than medial spiny neurons in the striatum, the consequence of which is a large striatopallidal convergence. The output side of the pallidum is the internal pallidum and the dopaminergic compact part (pars compacta) and GABAergic reticular part (pars reticulata) of the substantia nigra. The major target of the output GABAergic neurons in these structures is the subthalamic nucleus. In addition, the inhibitory terminals innervate the ventral and other nuclei of the thalamus.[17]

The similarity between the cerebellar and basal ganglia architectural organizations is striking. Very large numbers of parallel inhibitory loops are funneled back onto a relatively small, excitatory hub with widespread projections (i.e., deep cerebellar nuclei and the ventral thalamic nuclei, respectively). The best guess for the computation role of this arrangement is that the neurons in the loops provide the necessary calculation for precise spike timing for the numerically much smaller target neurons in these hubs. The strictly local organization of the loops can provide highly accurate temporal coordination for adjacent targets only (e.g., for high-precision coordination of neighboring muscles). Integration between

17. An excellent overview of the anatomical organization of the basal ganglia is Heimer et al. (1995). For the discussion of parallel computation in functionally segregated loops, see Alexander et al. (1986), Graybiel et al. (1994), and Haber (2003). Intrinsic connectivity is discussed in Koós and Tepper (1999) and Chang et al. (1981). The loops involving orbitofrontal, anterior cingulate, and dorsolateral prefrontal cortices may contribute to nonmotor functions (Bolam et al., 2000). It should be noted that the above description ignores the complex mosaic organization of neurochemical systems that are related to these neuroanatomical connections. For a thorough discussion of the segregation of the functional compartments, see Gerfen (1992). The dorsolateral vs. ventromedial functional distinctions are based mainly on the input-output connections. This applies to the core vs. shell divisions of the nucleus accumbens, as well (Záborszky et al., 1985).

nonadjacent calculations, when necessary, must occur downstream to the outputs. Alternatively, the calculations can proceed in parallel, and the precision of timing is due to the similar initiating conditions by the inputs.

Sustained Activity Requires Regenerative Feedback

A fundamental difference between the inhibition-dominated cerebellum and basal ganglia circuits, on the one hand, and cortical networks, on the other, is the inability of the former structures to support large-scale, self-organized spontaneous patterns.[18] This is best illustrated by the very low-amplitude local mean field potentials observed from the surface or the depth of the cerebellar cortex.[19] From the anatomical point of view, the low-amplitude activity is surprising, given the regular architectonics of the cerebellum and the parallel excitatory inputs it receives. On the basis of cytoarchitecture alone, one might expect to see local field responses as large as those seen in the hippocampus. This is indeed the case with electrical stimulation, when large numbers of neurons are synchronized by an external input.[20] However, in the absence of external synchronization, cerebellar or basal ganglia circuits cannot support spatially widespread synchrony. Supersynchronous, epileptic discharges never arise from the GABAergic-neurotransmission–dominated cerebellar or basal ganglia networks. In fact, it appears that the computation in the locally organized networks of these structures represents an antithesis of cortical performance, characterized by perpetual spontaneous activity and temporally coordinated patterns over wide spatial domains.[21]

Cell-attached and whole-cell recordings in anesthetized rats have shown that cerebellar granule cells are usually not spontaneously active *in vivo* and require excitatory mossy fiber synaptic inputs to fire. Inputs from the mossy fibers exhibit periods of rhythmicity in the 5–13 hertz range.[22] The inferior olive also provides

18. Cortical inputs and the subthalamic nucleus do provide excitation to striatal neurons, but this is not recurrent or reconstructive. Both sources of excitation generate feedforward inhibition.

19. Niedermeyer (2004) concludes that the cerebellar EEG is characterized predominantly by ultrafast, low-amplitude patterns, but the "electrocerebellogram is still insufficiently understood."

20. During synchronized inputs from either the brainstem or inferior olive, e.g., during generalized petit mal thalamocortical seizures, large-amplitude fields can be recorded from throughout the cerebellum, demonstrating that cerebellar circuits can generate extracellular currents, provided that synchrony is provided from outside (Kandel and Buzsáki, 1993).

21. Of course, the locally confined computation is the essence of these circuits. Balance and muscle coordination require instant and updated short responses. Sustained activity may be detrimental, since it would interfere with the precise tuning of muscles. Each cerebellar and basal ganglia module can provide computation with temporally high resolution without interference from distant modules. This high autonomy is more reminiscent of computer architectures than of the shared computation of the cerebral cortex.

22. Häusser and Clark (1997) and Häusser et al. (2004). Unfortunately, there are very few studies on the cerebellar and basal ganglia circuits during sleep, and it cannot be inferred to what extent activity is due to the synchronized inputs or to the internal circuitry (e.g., Andre and Arrighi, 2001).

a rhythmic input to the Purkinje cells in the same frequency range by way of the climbing fibers. In the absence of chemical neurotransmission, Purkinje cells do display continuous spiking, but these spikes are not coordinated across neurons. Even the isolated brainstem–cerebellar preparation, sustained *in vitro,* has no spontaneous population activity. However, this preparation responds with oscillations to the pharmacological challenge by the psychoactive plant alkaloid harmaline the same way it responds *in vivo.* The oscillation arises in the olivary network (10–12 hertz), which drives Purkinje cells. In turn, Purkinje cells generate rhythmic inhibitory potentials in the neurons of the deep cerebellar nuclei.[23] Individual neurons in the cerebellar nuclei fire remarkably rhythmically between 20 and 150 hertz during both waking and sleep states, but they seldom show population synchrony.[24]

Similarly, coordinated network activity in the basal ganglia neurons is provided by the cortical inputs, but oscillatory patterns remain highly localized. In the oculomotor region of the striatum in macaque monkeys, focal oscillations at 15–30 hertz pop in and out of synchrony as the monkey makes saccadic eye movements.[25] Similar local field oscillatory patterns have been described in the rat striatum, as well. However, individual neurons only exceptionally showed phase-locked spiking with the field, suggesting a noncoherent multifocal origin of the fast waves.[26]

Only Structures That Display Persistent Neuronal Activity and Involve Large Neuron Pools Support Consciousness

Although explaining the sufficient conditions for conscious behavior is not within our reach, we can at least begin to list the necessary requirements by examining the distinguishing features of the neuronal organizations that support it. The findings discussed above illustrate the important point that different anatomical architectures support different physiological functions. Although oscillations can arise from many types of networks, only special architectures, such as the cerebral cortex, can support spatially widespread oscillations at multiple temporal scales and

23. Llinás and Muhlethaler (1988).

24. The activity of Purkinje neurons is generated through an intrinsic mechanism, mainly through persistent Na^+ channels (Llinás and Sugimori , 1980; Nitz and Tononi; 2002). Individual Purkinje cells display strong metastability, switching between sustained firing and hyperpolarized states (Loewenstein et al., 2005). However, these state changes are not coordinated across distant Purkinje cells.

25. Courtemanche et al. (2003). For a summary of striatal rhythms, see Brown (2003) and Boraud et al. (2005).

26. Berke et al. (2004). Most neurons showed synchronous discharge with high-voltage spindles (Buzsáki et al., 1990), but these rhythms arise in the thalamocortical system, and striatal neurons simply respond to the cortical inputs. Importantly, the rhythm-generating substrate of Parkinsonian tremor, a cardinal symptom associated with a deficit of the basal ganglia, is the reticular nucleus–ventrobasal thalamus circuit.

with the consequent 1/*f*-type, self-organized criticality features. Global, collective decisions are needed for most cortical functions. Collective decisions, however, require cooperative actions of both neighboring and distant areas. Flexible cooperation among local and distant cell assemblies is believed to underlie the efficacy of cortical performance and is an essential ingredient for cognition, as well. One may therefore speculate that the ability of a network to generate sustained or persistent activity is the key for the emergence of conscious experience. If no long-range connectivity exists and/or if the activity cannot persist for a *sufficient amount of time,* locally generated activity cannot engage distant neurons; therefore, integration of information over a large neuronal space cannot take place. Regenerative activity requires positive, excitatory feedback, a critical ingredient conspicuously absent in cerebellar and basal ganglia circuits. Regenerative feedback can incorporate the past into the system's present state, and it threads the system through both time and space, thereby allowing input-induced perturbations to be compared with the effects of previous similar encounters. It is the reconstructive feedback and the sustained neuronal activity it supports that can place the inputs into context.

The most striking, yet perhaps the least appreciated, behavior of cortical networks is their regenerative, spontaneous activity. This self-generated neuronal activity is what is constantly added to the sensory inputs. Every spike, sensory evoked or spontaneous, in cortical principal cells can reach distant neurons. It is critical to recognize that there is not much else that one can investigate at the neuronal level in the brain besides stimulus-evoked and spontaneous brain activity. If spontaneous cortical activity is perturbed by a stimulus for a sufficiently long time in large enough neuronal space, it will be noticed; that is, we become aware of it. This spontaneous, self-organizing ability of cortical networks is what gives rise to originality and freedom in the brain.[27]

In contrast to the abstract and arcane problem of consciousness, the issues involved in the interaction between self-organized and evoked activity can be investigated empirically and systematically by comparing the lifetime and expansion of an input in neuronal space.[28] As discussed in previous Cycles, the same physical inputs engage neuronal populations of different sizes whether or not they are perceived, and their efficacy depends on the state of the brain.

Spontaneous activity alone does not give rise to consciousness, however. A

27. For my money, understanding the self-organizing ability of the brain is the most interesting challenge in science. Without such knowledge, it is hard to imagine how we will ever resolve the deepest mysteries of the intact and deranged brains.

28. E.g., Srinivasan et al. (1999). Unfortunately, EEG or MEG studies do not have the necessary spatial resolution to address these issues analytically. Massimini et al. (2005) studied the spread of evoked activity in response to transcranially induced magnetic stimuli in humans. The stimuli reset alpha oscillations and invaded large cortical areas during rest with eyes closed, as expected from the widespread nature of alpha oscillations (Makeig et al., 2002; Cycle 7). In contrast, the same stimuli evoked larger local field potentials during slow-wave sleep, but the size of the stimulus-affected neocortical territory was smaller compared to the resting state. This latter observation is in line with the well-known resistance of sleep-related oscillations to external perturbations.

brain grown *in vitro* with sensors attached but without an ability to move those sensors by the brain's output, as discussed in Cycle 8, cannot become conscious, in the sense that the neuronal responses evoked by the sensory inputs would not acquire or reflect meaning. Similar to the somatosensory system, which requires metric calibration through movement, and the dead-reckoning navigation system of the hippocampus, which has to be calibrated by explorative locomotion, consciousness also needs a calibration process. It is the brain's interactions with the body and the physical–social environment that provide stability and meaning to a subset of all possible spontaneous states of the brain. The brain gradually acquires its self-awareness by learning to predict the neuronal performance of other brains. In other words, acquisition of self-consciousness requires feedback from other brains. This process may be likened to being one of the protestors in a large demonstration. A special feeling arises from the realization that multitudes of others feel (resonate) the same way (with similar past histories, desires, etc). Self-consciousness has to be learned.

An explicit prediction of the above speculation is that large numbers of neurons with small-world-like connectivity can give rise to regenerative, spontaneous activity of the 1/*f* type, and that this self-organized activity is a potential source of consciousness.[29] An implicit prediction is that such a quality is not all-or-none but is graded and depends on the size of the network. The lack of long-range connections and intermittent local neuronal bursts in premature babies implies the absence of consciousness. Perinatal maturation of cortical anatomy and the emergence of 1/*f* cortical dynamics offer the proper substrate for the gradual emergence of self-awareness. Furthermore, these same properties grant consciousness to not only humans but also to other mammals, although to a lesser degree.[30] Consciousness is in the organization, although size also matters. As Sigmund Freud phrased it, anatomy, in this regard, is destiny. Cerebellum-type

29. Autonomous oscillations of non-REM sleep and anesthetic states are an antithesis of conscious awareness. These oscillations are deterministic and resistant to environmental or body inputs. Similar arguments can be made for the oscillations in the cerebral cortex that characterize sleep (Cycle 7). In contrast, the scale-free (1/*f* type) neocortical EEG of waking and REM-sleep reflects perpetual phase transitions brought about by the interference of multiple oscillators and characterized by high sensitivity to perturbation (Cycle 5). The 1/*f* complex nature of cerebral cortical activity may be the neurobiological expression of the integration consciousness index, Φ, of Tononi (2004).

30. *Quale* (e.g, feeling of a color) and feeling of the self are often distinguished as different qualities. In my view they are related "hard" problems because the difficult issue is the source of "feeling" rather than the difficulty in explaining the difference between color and self. Testing self-consciousness or self-awareness in nonhuman animals is quite difficult. Nevertheless, there is some agreement that visual self-recognition or self-identity is present in great apes. E.g., chimps can come to recognize dabs of paint on their foreheads in a mirror, placed there by the experimenter while the animals slept (Gallup, 1970). The existence of phenomenal consciousness, i.e., the phenomenological aspects of conscious experience (related to *qualia*), is more controversial (e.g., Nagel, 1974). One identifiable *quale* in most mammals is the feeling of pain. Although "feeling" can be only inferred from overt behavior, centrally acting pain-relieving drugs not only reduce the subjective feeling of pain in humans but also can eliminate the motor correlates of inferred pain in other mammals. Interest in animal consciousness not only is a philosophical issue but also has considerable moral significance.

organization can never give rise to conscious experience, no matter the size. On the other hand, the cerebral cortex, with its self-organized, persistent oscillations and global computational principles, can create qualities fundamentally different from those provided by input-dependent local processing. It may turn out that the rhythms of the brain are also the rhythms of the mind.[31]

31. A new story should begin here. It likely did not escape the reader's attention that rhythms, as reflections of global cortical computations, can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance. Rhythms are a robust phenotype that can be monitored and quantified objectively for the diagnosis and progression of psychiatric and neurological ailments. Although "rhythmopathies," "oscillopathies," and "dysrhythmias" have been discussed repeatedly over the years (John, 1977; Rensing et al., 1987; Llinás et al., 2005; Schnitzler and Gross, 2005), recent progress in the understanding of the mechanisms and neuronal content of brain rhythms infuses a new life into these old terms. Rhythms are affected by most psychotropic drugs, and testing their effects on neuronal oscillations will likely become a widespread tool in drug discovery.

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