THE DANA FOUNDATION'S

BRAINWORK

The Neuroscience Newsletter

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News FROM THE FRONTIER

••• Vaccine boosts activity of chemotherapy in brain cancer. Clinical trials show that patients with glioblastoma multiforme, a particularly aggressive brain cancer, survived longer if they were treated with a vaccine followed by chemotherapy than did those patients treated with either the vaccine or chemotherapy alone. The finding continues recent progress in immune treatments for brain tumors (see "Brain Tumor Researchers Let Slip the Immune Cells of War," May-June 2005 *BrainWork*).

The vaccine appears to kill off chemotherapy-resistant cells, leaving behind a population of cells that can be treated with chemotherapy, report John S. Yu, co-director of the Comprehensive Brain Tumor Program at Cedars-Sinai Medical Center in Los Angeles, and colleagues in the August issue of *Oncogene*.

To make the vaccine, dendritic cells were harvested from each patient's blood, grown in a dish that contained proteins from glioblastoma tumors, and then injected back into the patient's bloodstream. The process generates

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SPECIAL FOCUS: **NEUROIMAGING**

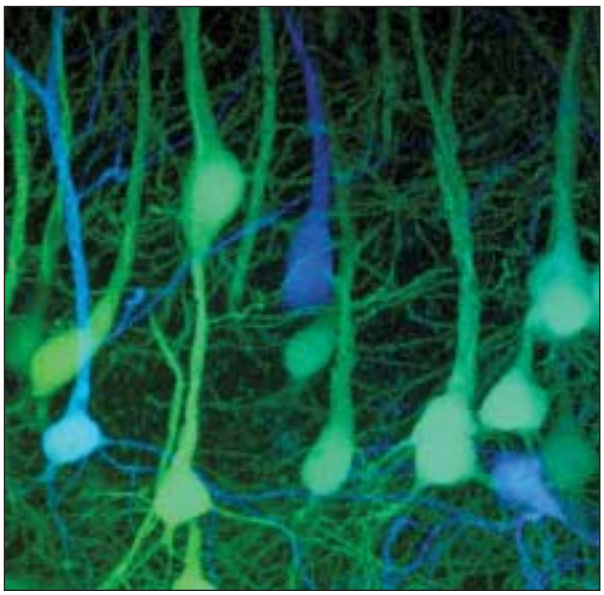
Peering into the Brain:

New Frontiers in Neural Imaging

BY BRENDA PATOINE

New technologies—and the innovative ways in which scientists have harnessed them—have driven advances in neural imaging beyond what any expert predicted 10 years ago. Ever more sophisticated images from brain scans and new microscopy techniques are offering a strikingly clear glimpse of what's going on underneath the bumpy surface of our skulls.

Some of the greatest excitement in neural imaging right now surrounds the fast-emerging frontier of optical imaging, or, more precisely, two-photon excitation microscopy combined with fluorescent dyes that label individual molecules in living tissue. Scientists are applying these tools to track brain function in living animals in real time, right down to the level of synaptic connections and beyond.



Green fluorescent protein, or GFP, is expressed in the visual cortex of a transgenic mouse, as shown in this two-photon microscopy image. This type of imaging is advancing scientists' understanding of the brain.

A recent meeting on neural imaging at Cold Spring Harbor Laboratory in New York was testimony to the results possible using so-called "light microscopy" approaches. A few dozen of the world's leading experts in imaging gathered to compare notes, debate technical hurdles, and share some of the most remarkable video and still images of mammalian brains in action.

Two-photon microscopes use longer wavelengths of light, supplied by lasers, to penetrate tissue more deeply and with less damage than other optical imaging modes. A critical advance that pushed the field forward was the identification and cloning of the gene for green fluorescent protein (GFP), reported in a landmark *Science* paper in 1994. GFP is a naturally

(Continued on page 2)

(NEURAL IMAGING, continued from page 1)

occurring protein that essentially makes cell tissue light up like a neon sign when viewed with light microscopy.

Roger Tsien at the University of California, San Diego, and others have developed a whole spectrum of GFP variants, a broad pallet of colors that neuroscientists worldwide are now using to characterize neuronal structure and activity to a degree never before possible.

'No Competition'

Among alternative methods, "there's no competition for optical imaging," says Karel Svoboda of Cold Spring Harbor, who co-chaired the meeting. "Using genetic tricks with GFP and its dozens of variants, you can now put into neurons fluorescent markers of structure, of specific molecules, or of cellular function. This has enabled a better understanding not only of the structural biology of the brain at the level of synaptic circuits, but also has begun to help us learn about the function of populations of neurons in the intact brain."

The Neuroscience Newsletter

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"The genetics has gotten to the point where you can target cells pretty precisely with a fluorescent protein," says David Kleinfeld, a University of California, San Diego, neurophysicist who attended the meeting. "You can go back to the same cell every time and determine its functional identity. Does the cell report the same sensory features time and time again, or does its role in a circuit evolve with experience? You can now study the same animals over time, which is particularly critical when you're studying brain development."

Grappling with Circuits

These new methods are also making a huge impact on systems neuroscience, which seeks to construct "wiring diagrams" that correlate brain activity to specific behaviors. Much of the Cold Spring Harbor meeting focused on the challenge of understanding neural circuits, Svoboda says.

"In the mammalian brain, you have a million upon millions of neurons," he says. "If you think of it from an engineering standpoint, the brain is an electrical signaling device, and neurons are the signaling units. Any engineer will tell you that if you want to understand a circuit, you need to have a circuit diagram. You not only need a list of components, but you also need to know how neurons connect with one another and with what probability." There has been good progress on the "parts list," but understanding the connection matrix is still at a "primitive stage," he says.

One reason: until now, the standard technique for constructing a diagram of a neural circuit had changed little since the late 1800s, when Spanish anatomist Santiago Ramon e Cajal pioneered it. The technique essentially involves staining single neurons, identifying where axons and dendrites overlap, and marking those junctures as synapses.

A problem with this approach, Svoboda says, is that "there's no functional context. You don't really know whether or not and to what extent these neurons 'synapse' onto one another." While electrical recording studies can measure activity across synaptic connections, Kleinfeld says optical imaging now makes it possible "to observe how different sensory and motor patterns sculpt and resculpt the connectivity."

Some of the most cutting-edge work with light microscopy involves finding ways to identify neuronal function in a manner that is rational, quantifiable, and reproducible. The ultimate goal is to use different types of GFP-based indicators of neuronal function in various types of neurons in order to understand how they interconnect and influence one another.

"What you're really after is to record something that tells you about the state of the neuron: is it sending an output signal or not; what are its input signals like; what is its sense of history?" says Kleinfeld. Each of these states can be understood by looking at specific physiological indicators that can now be visualized with optical imaging.

Josh Sanes, a neurobiologist and head of Harvard's new Center for Systems Neuroscience, describes his dream scenario: "to label 10, 20, 30 different neuronal types with different colors, and do it such a way that when the neuron fires it would change color." This would make it possible to track neural activity throughout the circuit, with different cell types and functional characteristics clearly demarcated. Then, individual cells or even genes could be turned off or on to understand their roles in the circuit.

Such studies are just beginning, and many technical hurdles remain. Still, Svoboda says, "We've made remarkable progress." For example, his group has pioneered *in vivo* imaging of neurons over long periods, even months at a time, something that was "just a pipe dream 10 years ago."

Birth of Modern Imaging

Such advances were unimaginable back in the 1970s, when the advent of computerized tomography (CT) scanning marked the beginning of the modern era of neural imaging. "CT was a remarkable advance, because it was the first time you could look into the brain of a living person," says Arthur Toga, who heads the Laboratory of Neuro

Imaging and Behavior: Reality Check

The visual appeal of imaging studies, coupled with their relevance to things people care about, such as memory and emotion, can leave the work open to less-than-critical interpretation. Experts say findings on imaging and human behavior come with a few caveats.

Marcus Raichle of the Washington University School of Medicine acknowledges that by the time discussions of what imaging can show enter the public arena, brain function has begun to sound overly localized. A good example is the so-called fusiform face area in the temporal lobe, considered by some researchers to be specialized for recognizing faces and by others to be part of a complex distributed network.

"By the time people read about this part of the brain, what they come away with is that it's the 'face area,'" Raichle observes, but that may be an oversimplification.

It's also important to remember that imaging is correlational. Ed Smith, cognitive neuroscientist at Columbia University, explains: "By themselves, imaging studies don't prove that a particular area is the source of a given mental process, only that it's active at the same time." To prove cause and effect, scientists are increasingly backing up results with studies of patients who have damage in the same area; a lesser degree of activation in these patients adds weight to the argument that the region is necessary to the behavior in question.

Smith also notes that time plays a role in imaging. Functional magnetic resonance imaging, or fMRI, for example, can distinguish events that occur a minimum of two seconds apart. Most of the mental tasks investigated in imaging studies take far less time. For example, naming a picture involves matching the picture to an internal memory bank, retrieving its name, and pronouncing the word. The entire process takes about half a second. More comprehensive views will take shape as whole-brain imaging studies, such as fMRI, are joined to "faster" measurements and with cellular studies in animals, such as two-photon microscopy.

—Elizabeth Norton Lasley

Imaging at the University of California, Los Angeles.

Magnetic resonance imaging (MRI) and positron emission tomography (PET) followed CT. These powerful tools have enabled an unprecedented look not only at the brain's anatomical structure, but also, in the case of PET and functional MRI (fMRI), at the patterns of brain activity that underlie mental functions and pathological states. Such "whole-brain" imaging modalities have transformed neuroscience research and are increasingly influencing the clinical practice of neurology, psychiatry, and neurosurgery.

PET and fMRI are the elder statesmen of neuroimaging. Not only have they become indispensable for basic research, but their capacity to show changes in oxygen and glucose metabolism indicative of neural activity has driven the burgeoning field of cognitive neuroscience, which seeks to understand higher-order brain functions and psychological states.

At the same time, new PET imaging agents—the radioisotopes that zero in on specific brain chemicals—have extended the uses of PET, making it possible to identify changes in dopamine receptors in Parkinson's disease, for example.

In terms of clinical practice, neuroimaging has undoubtedly had the greatest impact on neurosurgery. Brain scans are routinely used presurgically and, increasingly, during surgery to identify critical brain structures that must be avoided in the operation and to guide the surgeon's scalpel to a tumor or vascular occlusion. But imaging is also playing a greater role in neurology and psychiatry clinical practices.

One sign of this progression is the government's recent announcement that Medicare will cover the cost of PET scans in certain people suspected of having Alzheimer's disease, a recognition of PET's utility in differentiating Alzheimer's from other types of dementia. In October, the NIH launched a five-year, 50-site study designed to identify biological markers for Alzheimer's through brain imaging, with the ultimate goal of improving early diagnosis and intervention. (See "New Techniques Detect Alzheimer's Before Symptoms Develop," this issue.)

Integration Is Key

Toga encapsulates what he finds most exciting about the current state of neuroimaging in one word: integration. "We have made tremendous progress in terms of the technological advances to acquire images that describe one part of the brain or another," he says. Examples include diffusion tensor imaging, which processes MRI scans in a way that enables researchers to see the white tracts of neuronal axons, and new approaches to looking at vascular architecture and blood flow changes in the brain.

"What's now occurring is the application of complex computational strategies that extract more information out of the images that are acquired, giving you a much more comprehensive view of what's happening in a normal brain and what's going wrong in pathological conditions," Toga says. "So now we can take that data, 'massage' it, compare it against statistical and imaging databases, and apply a variety of visualization algorithms to look at it new ways."

Such progress would not have been possible without the integration of multiple disciplines, Toga says. "You have mathematicians, computer scientists, and related disciplines now working on these problems of imaging the brain. That's relatively new."

Coupled with technological advances, this unprecedented collaboration has spawned novel approaches to neural imaging and allowed scientists to look at age-old questions about the human mind in a whole new way.

"It's the great quest," Toga says. "The brain is the only organ in the body that makes us who we are, so we can't help but want to see if we can get a handle on that."

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Cha-Ching! Neural Processes Underlie Economic Decisions

BY ELIZABETH NORTON LASLEY

Since imaging technologies made their debut in the early 1990s, they have gone from providing colored pictures of specific brain areas to yielding valuable information about complex behavior. Such understanding is of importance not only to clinicians and psychotherapists but, perhaps surprisingly, to economists.

The laws of economics have traditionally discounted the brain, assigning values to observed behavior and assuming that everyone will act in his or her own best interest. "Economists have been happily ignorant of the brain and psychology, and until recently that's been fine because the brain processes underlying behavior weren't understood," says Colin Camerer, an economist at the California Institute of Technology. But humans are perplexing creatures who behave in irrational ways, and brain imaging is beginning to offer some explanations.

The Circuitry of Satisfaction

A central question in economics is why people want the things they want, or, in neuroscience terms, how the brain processes reward. Imaging studies show that in response to perceived reward, a brain region called the striatum is activated in remarkably specific ways.

The striatum comprises two tubular structures in a V shape located behind the eyes; its chief neurotransmitter is the well-known reward chemical, dopamine. In a study published May 11, 2005, in the *Journal of Neuroscience*, Brian Knutson and colleagues at Stanford University found that when a person considers the value of monetary gain, functional magnetic resonance imaging (fMRI) scans showed activation in the striatum. But when subjects weighed the likelihood of getting the reward, activity was strongest in the cortex, the outermost layer of the brain where "executive" processes like analysis and impulse control take place—specifically in a structure called the medial prefrontal cortex (mPFC).

"Someone whose mPFC is not well-developed might focus on the size of the reward rather than its probability and make bad decisions, like gambling or playing the lottery," says Knutson.

The striatum is involved in a less obvious type of reward known as altruistic punishment, which Knutson likens to inching forward in traffic just to prevent the red sports car that's been zipping along the shoulder from getting back in. In a study reported in the August 27, 2004, issue of *Science*, Ernst Fehr and colleagues at the University of Zurich asked subjects to play several rounds of a game in which one player entrusted another with money. The second player had the option of giving back half or keeping it all; if Player B kept the money, Player A could assign a monetary punishment, though sometimes at an additional cost, depending on the rules of that round.

Positron emission tomography (PET) scans showed activity in the striatum when players accepted cost penalties for the sake of giving stingy partners their comeuppance. Moreover, players with strongest activation in the striatum were willing to incur the greatest cost to see justice done.

"Altruistic punishment is probably a key element in explaining the unprecedented level of cooperation in human societies," the authors wrote, concluding that the anticipated satisfaction of meting out punishment activates reward-related brain pathways.

Model-building and the Caudate Nucleus

A part of the striatum known as the caudate nucleus seems to be involved in predicting others' behavior—an ability central to both cooperation and competition. In another game involving money exchange, a team headed by P. Read Montague of the Baylor College of Medicine, Houston, noted increasing activity in the caudate as players began to trust each other. (See "News from the Frontier," May-June 2005 *BrainWork*.)

One player, the investor, gave money to the other, the trustee; the trustee could return some, all, or none. As reported in the April 1, 2005, *Science*, fMRI scans showed that activity in the investor's caudate grew stronger when the trustee responded generously and the investor increased the subsequent payment. The signal from the striatum also began to appear sooner as the investor gained confidence in the trustee—in the final rounds, even before the investor's decision was made—indicating that the caudate was building a model of the other player's actions.

In this game the results of each round were known right away—the trustee's response appeared on the investor's computer screen. But Camerer, one of the study's authors, says the caudate may be able to build an internal sense of what others will do even without immediate feedback. Camerer and California Institute of Technology economist Meghana Bhatt devised a game in which one player had to predict another's choices from a row of pictures on a computer screen. Activity in the caudate grew stronger as the player guessed correctly, even though the player did not know the results until the end of the game.

The study, published online May 17, 2005, in *Games and Economic Behavior*, turned up another interesting finding: players with strong activation in a region known as the insula were less able to anticipate what others would do. Camerer says the insula is likely to be "all about me," and high activity in this area may make it difficult to think strategically by putting oneself in another's place.

Neuroscience for the Common Good

Some skeptics dismiss imaging for purposes like these as a high-tech form of phrenology, the 19th century parlor science that involved interpreting the bumps on a person's scalp. Montague counters: "Even if fMRI did nothing more than provide a detailed atlas of brain activity, it would be a huge contribution. But you can use it to

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New Techniques Detect Alzheimer's Before Symptoms Develop

BY THOMAS S. MAY

Being able to detect high blood pressure can help doctors treat the condition before it causes a stroke or other serious illness. Similarly, the ability to measure blood sugar allows for the diagnosis and control of diabetes before it causes irreversible damage to a patient's blood vessels, kidneys, or other organs.

Alzheimer's disease (AD), however, is usually diagnosed only after clinical symptoms, such as memory loss and confusion, become apparent—and even then a diagnosis cannot be made with complete certainty. In most cases, these symptoms develop 10 to 20 years after plaques of beta-amyloid peptide (Aβ) begin to accumulate inside a person's brain.

Now, with the help of some recently developed neuroimaging techniques, scientists can visualize Aβ inside the brain before the disease becomes debilitating. Using these new techniques could help doctors predict the course of the disease, gauge the efficacy of various treatments, and one day possibly prevent or even reverse cognitive decline.

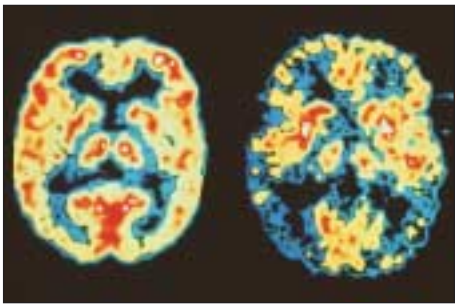
Pittsburgh Compound-B

The first chemical that has been used successfully to detect the presence of Aβ inside the brain of patients living with AD was developed by a group of researchers lead by William Klunk and Chet Mathis of the University of Pittsburgh. Named Pittsburgh Compound-B, or PIB for short, the chemical provides a tool to visualize beta-amyloid in the brain of living human subjects, with the help of positron emission tomography (PET). Mathis says the compound can help determine the efficacy of anti-amyloid drug therapies in clinical trials, and in the future, it may also be used as a diagnostic agent for AD.

Before the development of this brain imaging technology, AD could be diagnosed with certainty only by examining brain tissue itself during an autopsy, Mathis says. PIB is a variation of one of the tissue dyes used to positively diagnose AD after death, he explains. But he points out that, unlike the tissue dyes, PIB can enter the brain in living humans, bind to the beta-amyloid plaques, and be detected by PET.

Other Approaches

PET imaging with PIB has already been used in more than 200 clinical studies at 12 institutions worldwide, Mathis says. He admits, however, that it is unlikely to become a general diagnostic tool for at least another five years. The main reason for the wait is that conducting PET studies requires very expensive equipment.



Colored positron emission tomography (PET) scans show differences in the brain of a normal patient, left, and a patient with Alzheimer's disease (AD). The scan of the patient with AD indicates reduced function and blood flow in both sides of the brain, which is common in Alzheimer's.

In an attempt to make the detection of early AD more widely available using amyloid imaging, some of the same researchers who invented the PIB method are also developing a so-called hybrid tracer—a chemical that could be used not only with PET but with single-photon emission computed tomography (SPECT) as well.

"At present, SPECT is the key biomedical imaging modality that is available in most nuclear medicine departments around the world," says lead researcher Yanming Wang of the University of Illinois at Chicago. "We are extensively evaluating some dual agents in animal models, and completion of this project will allow us to identify a lead (preferred) compound that can potentially be used in human subjects in the near future for both PET and SPECT studies."

Another amyloid-imaging technique that has recently been tested in animals involves the use of magnetic resonance imaging (MRI) equipment. In a study published in the April 2005 issue of *Nature Neuroscience*, Makoto Higuchi and colleagues at the RIKEN Brain Science Institute in Japan injected a group of mice, specially bred with amyloid plaques in their brains, with a fluorine-labeled, amyloid-binding compound.

Using a high-magnetic-field MRI machine, the researchers were able to detect the amyloid plaques inside the living animals' brains. "This work is the first to visualize brain amyloid by fluorine-MRI, and it permits high-contrast imaging of the pathology with theoretically no background signals, because no fluorine atoms are present in the body," Higuchi says.

PET vs. SPECT vs. MRI

Magnetic resonance imaging has a higher resolution than PET, Higuchi adds, and there are other advantages to MRI: "It does not require radioactivity from the tracer, and thus can circumvent costly production and complex safety control of radioactive materials."

However, this technique cannot yet be applied to humans. "We need to inject the tracer at a considerably high dose, which might cause subacute or chronic toxicity," Higuchi says. Moreover, the MRI scanners most hospitals currently employ are not sensitive enough to detect signals from amyloid-binding fluorine.

Most hospitals are also unable to use the amyloid-imaging technique developed at the University of Pittsburgh, using PET scanners and the PIB compound, because of its high cost. Nevertheless, this method is already being utilized (in a few well-equipped centers) in the evaluation of some experimental treatments of AD.

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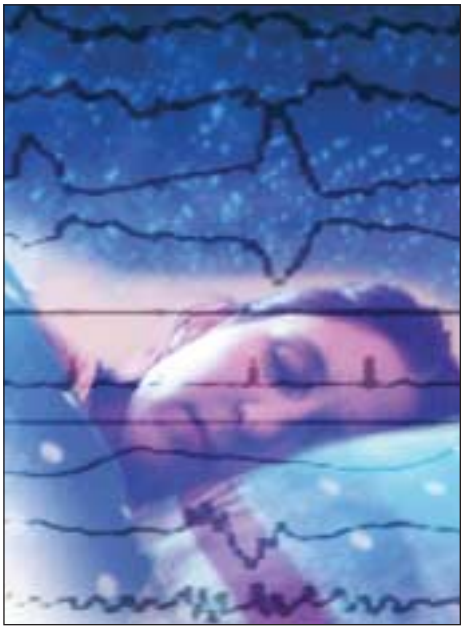
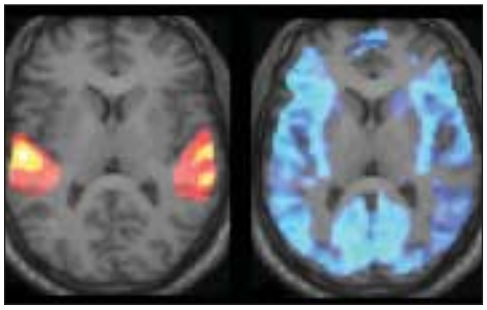
An Eye on Shut-Eye

BY RABIYA S. TUMA

Functional brain imaging is thought to be one of the most important discoveries in sleep research in the past 100 years. Researchers are using it to look at what happens in the whole brain during sleep, both in healthy individuals and in people who suffer sleep disturbances such as depression, sleep apnea, and insomnia.

Before brain imaging techniques developed, researchers relied on electroencephalograms, or EEGs, to learn about the different stages of sleep. EEGs detect the electrical activity in the brain through electrodes placed on a patient's scalp. The technique measures general patterns of brain activity, such as the speed of neural spikes, but is not sensitive enough to distinguish activity in different brain regions or in the deeper structures of the brain, below the cortex.





In the past, traces from an electroencephalogram, left, provided information about the stages of sleep. That method has been upstaged by functional magnetic resonance imaging, above, which provides a comparison of sensory processing during wakefulness, shown in the scan on the left, and light sleep. Sound signals are transmitted to the auditory cortex during wakefulness, as indicated by increased neural activity, but not during sleep.

Scientists know how sounds are processed in the brain when someone hears something while they are awake, with neural signals passing from the auditory nerve to the thalamus and then to the primary cortex, where the signals are processed. To find out what happens when someone is sleeping and hears a noise, Thomas Pollmächer, a lead investigator at the Max Planck Institute of Psychiatry in Munich, and colleagues are using functional magnetic resonance imaging, or fMRI, and EEG.

For these experiments, a volunteer lies in the MRI scanner with electrodes on his or her head. When the volunteer falls asleep, the researchers play a sound repeatedly. Significantly, the scientists do not detect activation in the thalamus or auditory cortex. The researchers interpret this lack of a strong signal to mean that the brain is actually trying to repress outside stimuli, as if trying to maintain sleep and prevent waking.

During rapid-eye movement sleep, or REM, during which most dreaming occurs, the group has observed a similar pattern in which the auditory cortex is quiet.

"The brain functions in a closed mode," Pollmächer says. "It tries to exclude external sensory information and reinforce internal signals."

That observation agrees with experimental data showing that sleep is important for reinforcing memories. While a person sleeps, the brain reviews the tasks or events of the day, storing them more securely than if the brain processed them only at the moment they occurred.

Meanwhile, Eric Nofzinger and colleagues at the Western Psychiatric Institute and Clinic in Pittsburgh are examining what regions of the brain are active during sleep in healthy and depressed volunteers and are helping to explain why patients with depression have a hard time sleeping.

In these experiments, volunteers sleep in a normal bedroom setting, with EEG electrodes attached and an intravenous (IV) needle in their arms. When volunteers reach a specified stage of sleep, the scientists inject a solution of radioactive glucose through the IV. They then wake the volunteers and put them in a positron emission tomography, or PET, scanner. Because the glucose goes to the cells that are most active, the team can see what regions of the brain were in use when they injected the solution.

During REM sleep depressed patients have an overactive limbic system, which controls emotions. "It's like they have a raw nerve, which is too easily overstimulated," Nofzinger says.

The team has started to look at what happens in patients who are depressed but receiving treatment. Nofzinger says they have preliminary results in these patients, and that although it is too early to draw conclusions, there are undoubtedly differences between untreated and treated patients.

Sleep is key to restoring an individual's brain power. If scientists can find out what healthy sleep looks like and what happens when it is disrupted—as occurs in depression—they may be able to correct it.

One striking observation, Pollmächer says, is what happens when his team uses EEG to see what is going on in a patient who complains about severe sleep disturbances: "The EEGs are almost non-remarkable. It could be that by looking at deeper regions [with imaging techniques] we will be able to understand why people perceive their sleep is so bad."

Rabiya S. Tuma is a science and medical writer in New York, N.Y.

News
FROM THE FRONTIER

(Continued from page 1)

dendritic cells that display proteins to immune cells, instructing them to kill other cells that have those proteins on their surfaces, including tumor cells.

"What we show now is that one of the antigens being targeted by the vaccine is TRP-2 [tyrosinase-related protein-2]," Yu says. "When treated with the vaccine, patients had much less antigen in their subsequent tumor than they did before treatment." Tumors that had less TRP-2 were more sensitive to chemotherapy than tumors with lots of TRP-2. The results suggest that targeting TRP-2 is important in treating glioblastomas.

••• Noise hides the signal in dyslexia. Children with dyslexia have trouble recognizing the sounds that make up words, but it is not clear why. One hypothesis is that dyslexic readers are less able to perceive visual cues that are processed by the magnocellular, or M, pathway of the visual system. However, new research suggests that the parvocellular, or P, pathway also plays a role.

The M pathway processes differences in brightness and signals that change rapidly in time, whereas the P pathway handles signals that have a high spatial frequency, such as narrow stripes. Anne Sperling, a postdoctoral fellow in neurology at Georgetown University Medical Center, and colleagues realized that the past experiments testing children's ability to process M signals had used visual patterns displayed on a "noisy" background, or displays where there was more going on than changes in the M signal. Sperling thought the problem might not be the M pathway *per se*, but rather an inability to distinguish the signal from the noise.

The researchers found that if they asked children to look for a pattern on a screen with a background resembling television static, the children with dyslexia required more contrast between the signal and background before they could detect an image. They had trouble seeing a pattern regardless of whether the visual cues were processed by the M pathway or the P pathways, according to the study, published in the July *Nature Neuroscience*.

The team concludes that the trouble differentiating signals from noise affects more than one pathway, and may even involve other sensory systems. "Anything we can do to jack up the volume" on the important signals may help children with dyslexia, Sperling concludes.

•••Blocking opiate receptors interferes with nicotine reward. When a smoker lights up, nicotine in the cigarette turns on reward pathways in the brain, providing a sense of pleasure. Researchers know how nicotine triggers the dopamine-responsive reward pathway, and now scientists at the University of Pennsylvania have found how nicotine stimulates the opioid pathway.

The team reports in the June 16 issue of *Neuron* that after conditioning, environmental cues were enough to trigger gene activity in the opioid pathway. When mice were given repeated nicotine injections in a cage distinct from their home cage, then placed in the injection cage but not given nicotine, the opioid pathway was activated. When given a choice, the mice preferred the injection cage.

Significantly, both the nicotine- and environment-induced opioid responses were blocked by pretreatment with an opioid inhibitor. After this treatment, the mice lost interest in the injection cage.

"We can block the molecular mechanisms and block the behavior," says lead author Julie Blendy, an assistant professor of pharmacology. That suggests opioid inhibitors might help people stop smoking by breaking the link between environmental triggers and reward sensations.

•••Controlling emotional feedback is key to depression. People with anxiety disorders or depression complain not so much about the emotion itself as its unceasing nature, says Daniel Weinberger of the National Institute of Mental Health. Now he and his colleagues may have found why their experience is continuous, according to work published in the June issue of *Nature Neuroscience*.

Scientists know that the serotonin transporter gene, which encodes a key protein for neurotransmission in the brain, comes in a long form and a short form. People who have the short form are susceptible to developing depression or anxiety, though the gene does not actually cause it.

To find out how the short form affects emotional health, Weinberger's team looked at 94 healthy individuals, some who have each form. Using brain imaging techniques, they found that two regions involved in emotional responses, the amygdala and the cingulate, were smaller in people with the short gene. Also, the neural circuits connecting the amygdala and the cingulate were weaker in people with the short form than in those with the long one.

That is important, says Weinberger, because the amygdala controls a person's response to fearful situations, evaluating whether they should react or not, and then the cingulate vets the amygdala's response. If a fear signal put out by the amygdala is not justified, the cingulate turns it off. But in people with the short form of the gene, the cingulate is not able to perform this editing function as effectively, so it is as if the amygdala is going off all the time.

"If you can't shut off fear, it is much worse than just feeling it for the first time," Weinberger says. The new evidence suggests that this phenomenon happens in people with the short gene, which would explain why they are more prone to depression and anxiety.

—R.T.

(ECONOMICS, continued from page 4)

understand how people think, and, in many cases, to predict what they'll do."

This idea may suggest some evil conglomerate peering into consumers' brains and exploiting their neural circuitry for profit. But the possibilities of imaging can be viewed the other way around. Aside from what Knutson cites as the obvious difficulty of getting the consumer into the scanner, Camerer believes that with a better understanding of brain and behavior, economists can help people make better choices—both about immediate purchases and long-term financial planning. Such choices might lower the estimated $5,000-per-household credit card debt, or lower the number of personal bankruptcies from the 1.5 million filed in 2004.

Finding ways to better integrate cortical and striatal areas might help people defer gratification and grasp the realities of compound interest. One day, insolvency might even be a treatable disorder.

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(ALZHEIMER'S, continued from page 5)

Although PET has a higher resolution than SPECT, it is very unlikely that medical insurance companies will pay for PET scans to diagnose AD in the foreseeable future, Wang says. Successful development of a hybrid tracer, which could be used with either PET or SPECT, "would bridge the gap between the two imaging modalities," he argues, and the clinical application of such a dual tracer "could be streamlined from the development stages in research laboratories directly to patients in clinics worldwide."

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