Finding coherence in spontaneous oscillations

Patrick J Drew, Jeff H Duyn, Eugene Golanov & David Kleinfeld

Spontaneous ultra-slow oscillations in brain signals are ubiquitous, although their source and function remain unknown. A new study now reports that this activity is correlated between functionally related areas across hemispheres in humans.

Although perception and action occur on the subsecond time scale, it has long been recognized that cortex also shows variable electrical activity on the 1–100-s time scale. What function does this ultra-slow oscillation serve? In this issue, Nir *et al.*[1] show that such ultra-slow activity in humans is correlated between functionally related areas of both hemispheres. This could be a signature of intercortical communication or a consequence of common subcortical modulation. The answer also has implications for the use of blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI) to deduce connectivity between brain regions.

With the emphasis in modern systems neuroscience on the extreme temporal precision of neuronal spiking, it is easy to overlook the slower electrical dynamics of the nervous system. There is extensive evidence that neuronal activity undergoes slow and periodic modulation at rates in the 1–100-s time scale (**Table 1**). Such ultra-slow activity has been reported in terms of a long tail in the interspike interval distribution of spike trains in the auditory system[2] and as a long tail in the correlation in the number of spikes emitted per stimulus in behaving monkeys[3]. Ultra-slow activity is also seen as a systematic variation in the power of the local field potential (LFP), a measure of spatially restricted and temporally coherent extracellular current flow, in monkey cortex[4]. Now, a consortium of investigators from Israel and the United States reports on a unique set of experiments in which they were able to identify intra- and interhemispheric coherence in electrical activity over long time scales, that is, 1–1,000 s, in awake and sleeping humans[1]. Their findings suggest that it may be possible in the future to assess whether ultra-slow electrical phenomena are related to cognitive processes.

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Table 1 Ultra-slow electrical dynamics in mammalian central nervous systems

Observation	Species	Magnitude of time scale
Graded persistent activity in entorhinal and prefrontal cortical neurons	Rat	1 to 100 s
Slow oscillation in cortical slices *in vitro*	Ferret	1 s
Slow oscillation in isolated cortical slabs *in vivo*	Cat	1 to 100 s
Slow variation in intracellular potentials of cortical and thalamic neurons	Cat	1 to 10 s
Spike trains in auditory and optic nerves[2]	Cat	0.1 to 100 s
Persistent electrical activity in the vestibular ocular reflex	Monkey	10 s
Spike trains along higher visual areas in cortex	Monkey	0.1 to 10 s
Persistent electrical activity in working memory	Monkey	1 to 10 s
Intrahemispheric correlation of the power in the ECoG (δ and γ waves)[4]	Monkey	0.1 to 100 s
Correlation of spike counts for individual neurons across sequential stimuli[3]	Monkey	100 s
Persistence of power in ECoG and MEG α-waves	Human	1 to 1000 s
Persistence of power in slow ECoG waves during sleep	Human	10 to 100 s
Interhemispheric correlation of both spike rates and power in ECoG and LFP γ-waves[1]	Human	1 to 100 s

Using pre-operative human volunteer patients, Nir *et al.*[1] carried out bilateral recordings of multi-unit spike waveforms and LFPs from auditory cortex, along with electrocorticograms (ECoG), a measure of spatially extended and temporally coherent extracellular current flow, from neighboring cortical regions. The authors primarily focused their analysis on γ-band oscillations of the LFP in auditory cortices (**Fig. 1a**); the frequency content of this band lies nominally between 40 and 90 Hz. A spectrogram of the LFP for signals acquired while a subject was in non–rapid eye movement sleep showed that the power in the γ-band is slowly modulated (**Fig. 1b,c**). The 'second spectrum', defined as the spectrum of the modulation in power for a given frequency band, showed multiple peaks whose center frequencies were on the order of 10^{-1} Hz (**Fig. 1d,e**). These modulations were present during both states of sleep and states of wakefulness; in the latter case, power at the lowest frequencies was greater during rest than during periods of auditory stimulation.

Is the modulation in γ-band power correlated in or across hemispheres? Their ability to simultaneously acquire signals at many sites allowed Nir *et al.*[1] to compute the coherence between signals at spatially adjacent regions as well as at functionally linked areas of opposing hemispheres. Interestingly, although the spike times and LFPs *per se* were not coincident across hemispheres, there was substantial coherence in the modulation of the spike rate and in the second spectrum of the LFP of γ-band oscillations. During rest, for example, there is a relatively large and positive correlation coefficient of 0.6 between ultra-slow signals from contralateral auditory areas, as compared with much smaller correlation coefficients between signals from auditory and nonauditory areas.

How are the ultra-slow variations in electrical activity linked across cortex? Although Nir *et al.*[1] do not provide direct evidence for a mechanism, previous studies of γ-band oscillations on short time scales (that is, 0.1–1 s) have reported stimulus-linked synchrony across hemispheres that is mediated through callosal connections[5] (**Fig. 2a**), which could conceivably underlie correlations of ultra-slow signals. An alternative, albeit nonexclusive, origin for the electrical covariations observed by Nir *et al.*[1] is modulatory drive from subcortical regions (**Fig. 2b**). It is known that subcortical modulatory systems are differentially engaged during different behavioral states, for example, resting versus attentive; thus, different patterns of cortical activation may reflect differential drive from modulatory centers. These inputs may even be functionally mapped, as cholinergic neurons in the basal forebrain innervate discrete areas of cortex, suggesting that the drive from subcortical areas may not be global but is probably targeted.

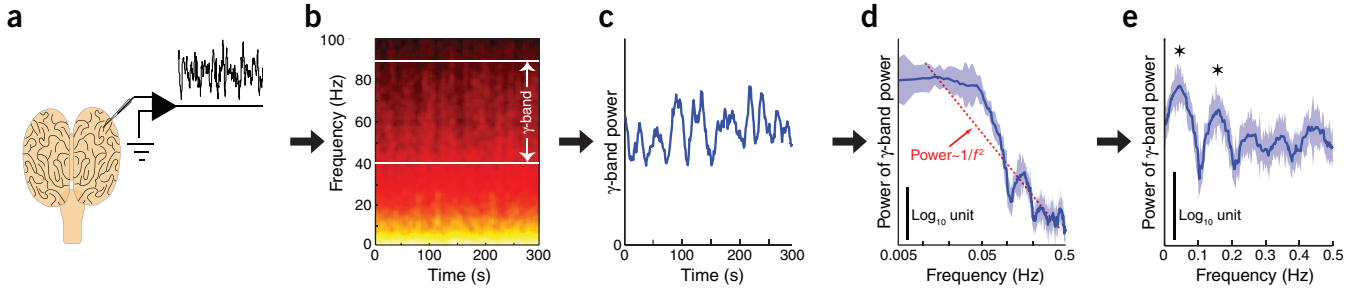

Figure 1 Measurements and analysis of ultra-slow variations in the power of the human γ-band. (**a**) The LFP was obtained during stage 2 sleep. (**b**) Spectrogram of the LFP (window = 10 s, overlap = 1.0 s,bandwidth = 1.5 Hz). Color scale maps the logarithm of power from black/red (low) to white/yellow (high). Note the slow variation in power in the 40–90 Hz γ-band. (**c**) Time series of the variation of integrated power in the γ-band of the LFP. (**d**) Spectrum of the time series in **c**, referred to as the second spectrum of the γ-band LFP (bandwidth = 0.025 Hz). The blue stripe represents the 95 % confidence interval. (**e**) Spectrum of the derivative of the time series in c as a means to remove a $1/f^2$ trend in the spectrum. * indicates a significant peak ($P < 0.01$). Our re-analysis of a single trace, kindly supplied by Y. Nir and R. Malach, used multi-taper spectral estimates available as MatLab-based routines at www.chronux.org.

The interpretation of γ-band oscillations in cortex, and variation in these oscillations, is a topic of lively discussion among neuroscientists and psychologists. Some investigators have attributed spatial coherence of γ-band oscillations to subconscious computations or even consciousness. Although Nir *et al.*[1] do not refute this possibility, they found that the cross-hemispheric correlations in the ultra-slow modulation of γ-band power are stronger during sleep states than during wakefulness. This increase is not inconsistent with cholinergic activation of cortex by subcortical input[6]. However, it should be noted that although ultra-slow dynamics may represent a reverberation in electrical activity, they may also result from biophysical mechanisms at the level of single cells. Neurons in entorhinal and prefrontal cortex can have multistable, persistent firing rates. At the molecular level, multiple types of ion channels show depolarization-induced changes in recovery time constants that last up to hundreds of seconds[7]. Finally, spontaneous synaptic release shows correlations over a multiplicity of long time scales[8]. The formulation of a robust model for ultra-slow oscillations in term of these and other biophysical phenomena remains a challenge.

Ultra-slow modulation of cortex-based BOLD fMRI signals occurs on the same time scale as the ultra-slow electrical activity in cortex[9]. Nir *et al.*[1] postulate that the coherence in ultra-slow modulation of the second spectrum of the γ-band is a strong candidate for the drive of these ultra-slow modulations in the BOLD fMRI signal. The patterns of activation in the BOLD fMRI experiments have an apparent overlap with anatomical boundaries of different functional areas in the brain[9]. Tempting as it may be to link the ultra-slow oscillations observed with BOLD fMRI to underlying electrical activity in cortex, a viable alternative hypothesis is that the BOLD fMRI signal reflects intrinsic fluctuations in vascular dynamics[10]. Notably, isolated arteries dilate and constrict on this time scale[11]. Fluctuations in the BOLD fMRI signal below 0.1 Hz are known to be driven by cardiac and respiratory cycles[12] and end-tidal CO_2 levels[13]. Finally, as basal blood flow and the magnitude of neurovascular coupling can depend considerably on the cortical state[14], comparing BOLD fMRI and electrical signals across different sleep and wakeful states is problematic.

An intriguing possible common source for cortical blood flow and electrical modulations is the rostral ventrolateral medulla (RVLM)[15]. Stimulation of the RVLM causes bilateral activation of cortex thorough thalamic relays that, as a result of their spatial map, could activate limited portions of cortex (**Fig. 2c**). RVLM neurons are also sensitive to oxygen levels, raising the possibility that modulations in RVLM output, and thus changes in cortical blood flow and activity, are slaved to fluctuations in breathing and blood oxygenation. This suggests the need for a new experiment to reveal whether RVLM is the driver of spatially coherent resting-state activity. This could be realized by simultaneous observation of blood flow and electrical activity across several cortical sites in response to both spontaneous and stimulated activity in the RVLM.

The ultra-slow variations in spike rate and power in the field potential appear to be ubiquitous in mammalian nervous systems (**Table 1**). Regardless of their origin, it is important to establish in future experiments what relation, if any, these coherent modulations have to cognitive processes. They may represent subconscious thought, yet still influence decision making and motor output. The answer to this question will depend of the continued cooperation of preoperative

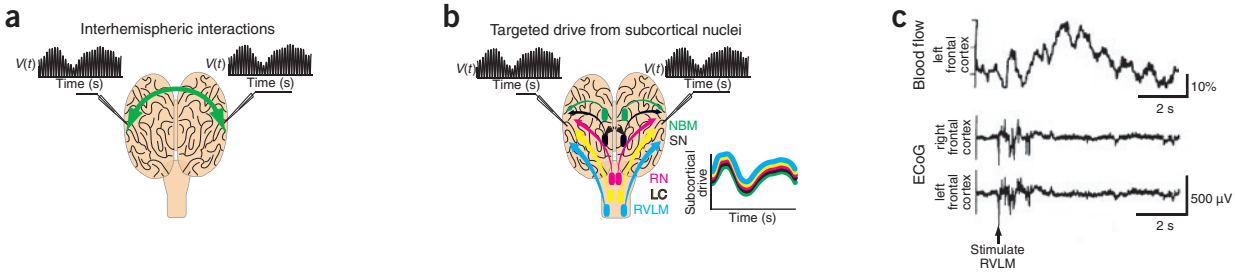

Figure 2 Two levels of interaction, with supporting data, that can lead to synchronous electrical activity across hemispheres. (**a**) Synchrony mediated by intercortical connections that course through the white matter of the corpus collosum. These are invariably, but not exclusively, mapped between similar areas with similar function. (**b**) Synchrony mediated by common input from brainstem and midbrain areas. dRN = dorsal Raphe nucleus, LC = locus coeruleus, NBM = nucleus basalis magnocellularis, RVLM = rostral ventrolateral medulla, SN = substantia nigra. All areas are known to form patterned input to cortex. Neurons in the SN form indirect interhemispheric connections. (**c**) Measurements that demonstrate the role of RVLM in driving bilateral changes to the ECoG and ipsilateral changes to blood flow in cortex[15].

human patients. The work of Nir *et al.*[1] shows that intracranial electrical recordings from these volunteers are a valuable methodological bridge between human and animal studies, bringing cognition and physiology closer together.

Note: the views expressed here are those of the authors and do not represent those of the US National Institutes of Health or the US Government. No official support or endorsement by the US National Institutes of Health is intended or should be inferred.

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Rhythms of memory

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Mitogen-activated Protein Kinases (MAPKs) are critical for the formation of stable long-term memories. New work shows that circadian MAPK activity cycling is important in the formation of new hippocampus-dependent memories.

Humans have an amazing capacity for storing learned information with high fidelity for long periods of time, but how are long-term memories stabilized and rendered permanent? In the earliest days of memory studies, 'reverberating circuit' models posited that continual, ongoing feedback loops of actively firing neurons maintained memory. Over time, these models were largely discarded for explaining long-term memory, as a result of the stability of long-term memory in the face of things such as deep general anesthesia, which globally diminishes CNS firing activity. The idea of reverberating circuits of neurons, repetitively firing action potentials as a device for storing many thousands of discrete memories, therefore seems untenable[1]. Instead, models of long-term memory storage that posit lasting, stable (or self-reinforcing) molecular changes at the synaptic and cellular level as the fundamental unit of memory persistence (the engram) seem more likely. In particular, many models propose that learning-induced alterations in gene expression and protein synthesis trigger lasting changes in cellular and synaptic properties as the basis for memory persistence[2]. The altered cellular and synaptic properties, subserved by persisting molecular changes, are read out as memories by recall mechanisms acutely triggering activity through the circuit in which the changes reside.

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Now a study by Eckel-Mahon *et al.*[3] in this issue of *Nature Neuroscience* may necessitate a refinement of the molecule-based model. In this study, Eckel-Mahon *et al.* make a series of observations that suggest that circadian cycling of the activity of the extracellular signal–regulated kinase (ERK) isoform of MAPK profoundly regulates the capacity of novel experiences to trigger lasting memory formation. Even more surprisingly, their observations suggest that ongoing circadian cycling of ERK activation in the hippocampus is necessary for long-term memory stability; that is, repetitive reactivation of signaling cascades that were used in the initial formation of a memory is required for the persistence of that memory. Their work suggests that ongoing cyclical reactivation of memory-associated signaling cascades are a necessary part of the memory stabilization and storage mechanism. This is somewhat reminiscent of the earlier reverberating circuit concept, except that the reverberating entity is a molecular signal transduction cascade, rather than a group of neurons.

Eckel-Mahon *et al.*[3] carried out an impressive series of biochemical and behavioral assays to determine whether hippocampal MAPK oscillations are necessary for long-term memory. In mice that were kept under normal light/dark conditions, the authors first observed that ERK activity in the hippocampus oscillated during a 24-h period, with a peak in levels during the light phase (the subjective day) being followed by a trough during the dark phase (the subjective night). Interestingly, the cycling of ERK activity showed regional specificity in the hippocampus, as it was present in regions CA1 and CA3, but was not present in the dentate gyrus. Moreover, this pattern of activity was not exclusive to ERK. The authors found that MEK, Ras and cAMP, all upstream regulators of ERK activity, likewise showed a cycling of activity (**Fig. 1**). Furthermore, they observed that phosphorylation of CREB, which is a downstream target of ERK and is necessary for gene transcription, also oscillated during a 24-h period, indicating that MAPK signaling activity oscillates in the hippocampus. But is this a circadian oscillation?

By definition, circadian rhythms are intrinsically driven and must be able to persist under constant external environmental conditions with a period of about 24 h. To address whether these oscillations are truly reminiscent of a circadian rhythm or whether they are merely responses to external periodicity cues (such as light), the authors kept mice in constant darkness for several days and then examined whether ERK underwent circadian oscillations. Indeed, in the absence of light, they found that ERK oscillated over a 24-h period.

ERK activation in the hippocampus has long been championed for its pivotal role in learning and memory. To determine whether the circadian oscillations of ERK activity were functionally relevant to an animal's ability to form new memories, the authors tested their mice in a contextual fear conditioning task. Contextual fear conditioning is a learning and memory procedure in which an animal is placed into a novel context and then presented with a series of mild foot shocks (**Fig. 1**). The animal then forms an association between the context and the aversive stimulus. Memory of this experience is then assessed 24 h later by placing the animal back into this context and measuring freezing behavior,