

# A BOLD window into brain waves

David Balduzzi, Brady A. Riedner, and Giulio Tononi\*

Department of Psychiatry, University of Wisconsin, Madison, WI 53705

The brain is never inactive. Neurons fire at leisurely rates most of the time, even in sleep (1), although occasionally they fire more intensely, for example, when presented with certain stimuli. Coordinated changes in the activity and excitability of many neurons underlie spontaneous fluctuations in the electroencephalogram (EEG), first observed almost a century ago. These fluctuations can be very slow (infraslow oscillations, <0.1 Hz; slow oscillations, <1 Hz; and slow waves or delta waves, 1–4 Hz), intermediate (theta, 4–8 Hz; alpha, 8–12 Hz; and beta, 13–20 Hz), and fast (gamma, >30 Hz). Moreover, slower fluctuations appear to group and modulate faster ones (1, 2). The BOLD signal underlying functional magnetic resonance imaging (fMRI) also exhibits spontaneous fluctuations at the timescale of tens of seconds (infraslow, <0.1 Hz), which occurs at all times, during task-performance as well as during quiet wakefulness, rapid eye movement (REM) sleep, and non-REM sleep (NREM). Although the precise mechanism underlying the BOLD signal is still being investigated (3–5), it is becoming clear that spontaneous BOLD fluctuations are not just noise, but are tied to fluctuations in neural activity. In this issue of PNAS, He *et al.* (6) have been able to directly investigate the relationship between BOLD fluctuations and fluctuations in the brain's electrical activity in human subjects.

He *et al.* (6) took advantage of the seminal observation by Biswal *et al.* (7) that spontaneous BOLD fluctuations in regions belonging to the same functional system are strongly correlated. As expected, He *et al.* saw that fMRI BOLD fluctuations were strongly correlated among regions within the sensorimotor system, but much less between sensorimotor regions and control regions (non-sensorimotor). The twist was that they did the fMRI recordings in subjects who had been implanted with intracranial electrocorticographic (ECoG) electrodes to record regional EEG signals (to localize epileptic foci). In a separate session, He *et al.* examined correlations in EEG signals between different regions. They found that, just like the BOLD fluctuations, infraslow and slow fluctuations in the EEG signal from sensorimotor-sensorimotor pairs of electrodes were positively correlated, whereas signals from sensorimotor-control pairs were not.

Moreover, the correlation persisted across arousal states: in waking, NREM, and REM sleep. Finally, using several statistical approaches, they found a remarkable correspondence between regional correlations in the infraslow BOLD signal and regional correlations in the infraslow-slow EEG signal (<0.5 Hz or 1–4 Hz). Notably, another report has just appeared showing that mirror sites

## Spontaneous BOLD fluctuations are not just noise, but are tied to fluctuations in neural activity.

of auditory cortex across the two hemispheres, which show correlated BOLD activity, also show correlated infraslow EEG fluctuations recorded with ECoG electrodes (8). In this case, the correlated fluctuations reflected infraslow changes in EEG power in the gamma range [however, no significant correlations were found for slow ECoG frequencies (1–4 Hz)].

### Where Do Infraslow Fluctuations Come from?

The results of He *et al.* (6) highlight several issues of general relevance in neuroscience. Although infraslow fluctuations are a prominent, constant feature of both BOLD and EEG signals, we still do not know where they originate. One possibility is that they reflect diffuse input from a subcortical source that is fluctuating in the infraslow range. For example, the firing of neurons in the midbrain reticular formation waxes and wanes with a period of  $\approx 10$  s during both wakefulness and sleep (9). Alternatively, neurons may slowly modulate their level of activity because of intrinsic changes in excitability, in the activity of ionic pumps, of neurotransmitter transporters, and of glial cells (2). Last, modeling the overall organization of corticocortical connectivity suggests that infraslow, system-level fluctuations in activity may be an emergent network property, not reducible to properties of individual neurons (10).

### What Wires Together Fires Together

Whatever the source of infraslow fluctuations, the He *et al.* study (6) makes it

clear that both BOLD and ECoG fluctuations display a pattern of regional correlations, or *functional connectivity*, which closely reflects those regions' anatomical connectivity (11, 12). Inverting a well known adagio, what wires together, fires together. Indeed, it seems that it could not be otherwise. If neurons are connected in a certain way, and if they are spontaneously active, functional connectivity is bound to reflect anatomical connectivity, just like traffic patterns must reflect the underlying roadmap. For example, because sensorimotor regions are more strongly connected to regions within the sensorimotor system, rather than without, if spontaneous activity in a sensorimotor area slowly fluctuates up for whatever reason, it will tend to increase firing in other sensorimotor areas more reliably than elsewhere, leading to increased functional connectivity. The wire together–fire together principle is bound to apply at multiple spatial and temporal scales. Consider neurons that are coactivated during learning tasks and become more strongly connected, in line with Hebbian principles (fire together, wire together). After learning, the same neurons show an increase in correlated firing when they are spontaneously active, both in quiet wakefulness and during sleep (wire together, fire together) (13, 14).

### What Is Spontaneous Activity for, and Is It a Distinct Mode?

Whatever the significance of infraslow fluctuations, the He *et al.* study (6) once more raises the question of what might be the role of spontaneous activity in the adult brain. The steady depolarization and firing of neurons, even when the brain is supposedly “at rest,” also called the “default mode” of activity (15), consumes approximately two-thirds of the brain's already disproportionate energy budget (16), so it better do something useful. For instance, spontaneous activity may be important for the brain's trillions of synapses, perhaps by keeping them exercised or consolidating and renormalizing their strength. Another notion is that spontaneous activity

Author contributions: D.B., B.R., and G.T. wrote the paper.

The authors declare no conflict of interest.

See companion article on page 16039.

\*To whom correspondence should be addressed. E-mail: gtononi@wisc.edu.

© 2008 by The National Academy of Sciences of the USA

may be necessary to maintain a fluid state of readiness that allows the cortex to rapidly enter any of a number of available states or firing patterns—a kind of metastability (17). Theoretical work suggests that the repertoire of available states is maximal under moderate spontaneous activity, and shrinks dramatically with either complete inactivity or hyperactivity (18). But what kind of neural states? One possibility is that the cortex is like a sea undulating gently, and that evoked or task-related responses would be like small ripples on its surface. This possibility is consistent with fMRI studies, because spontaneous slow fluctuations in BOLD are as large or larger than those evoked by stimuli (11). Also, it would fit nicely with the trial-to-trial variability of behavioral responses (19). Another possibility is that there are distinct modes of neuronal activity, such as a READY mode and a GO mode (and possibly an inhibited, STOP mode). Spontaneous activity would then be the READY mode of neuronal firing signaling the absence of preferred stimuli (an ongoing, low-level buzz). By contrast, in the GO mode, neurons, or local populations of neurons, would signal the presence of a preferred stimulus by firing at much higher

rates for short periods of time (a brief and loud shout). Unit recording studies have provided plenty of evidence that neurons respond strongly and distinctly to specific stimuli. In this view, the cortex would be more like a sea pierced by sharp islands. On the other hand, the slow hemodynamic response function underlying the BOLD signal may make fMRI partly blind to the distinction between slow, low-amplitude fluctuations in firing and fast, high-amplitude bursts of activity (4). If there are two modes of neural activity, it bears keeping in mind that neurons in the READY mode would be as necessary as neurons in the GO mode in specifying different cognitive states, just as the background is as necessary as the foreground.

### Gamma and Consciousness

Gamma activity has often been singled out as being especially relevant to consciousness, and just as often it has been mired in methodological controversies (20). In their article, He *et al.* (6), taking advantage of clean intracranial signals, report that correlations between pairs of regions in terms of BOLD signal, and correlations in EEG power in the gamma range (50–100 Hz), were themselves correlated. However, they

were correlated only in wakefulness and REM sleep, but not in deep NREM sleep. Because deep NREM sleep is the time when consciousness tends to fade, maybe the drop in gamma power correlations has something to do with the drop of consciousness. However, it may well be that the drop in gamma power correlations is just a symptom of something more fundamental. During deep NREM sleep, the spontaneous activity of neurons throughout the cortex is repeatedly interrupted, after just a few hundred milliseconds, by brief DOWN states during which neurons become profoundly hyperpolarized (1). This bistability of neurons, due to changes in neuromodulators, is likely to make it difficult for correlations in gamma power to establish themselves across distant brain regions, hence accounting for their symptomatic decrease. The same bistability, by reducing the number of available states, may be responsible for the fading of consciousness during deep NREM sleep, in contrast to the metastability of wakefulness and REM sleep. So, although the brain may always be on, it may not always be ready.

**ACKNOWLEDGMENTS.** This work was supported by National Institutes of Health Director's Pioneer Award and the J.S. McDonnell Foundation.

1. Steriade M, Timofeev I, Grenier F (2001) Natural waking and sleep states: A view from inside neocortical neurons. *J Neurophysiol* 85:1969–1985.
2. Vanhatalo S, *et al.* (2004) Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *Proc Natl Acad Sci USA* 101:5053–5057.
3. Viswanathan A, Freeman RD (2007) Neurometabolic coupling in cerebral cortex reflects synaptic more than spiking activity. *Nature Neurosci* 10:1308–1312.
4. Nir Y, Dinstein I, Malach R, Heeger DJ (2008) BOLD and spiking activity. *Nature Neurosci* 11:523–524; author reply 524.
5. Logothetis NK (2008) What we can do and what we cannot do with fMRI. *Nature* 453:869–878.
6. He BJ, Snyder AZ, Zempel JM, Smyth MD, Raichle M (2008) Electrophysiological correlates of the brain's intrinsic large-scale functional architecture. *Proc Natl Acad Sci USA* 105:16039–16044.
7. Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 34:537–541.
8. Nir Y, *et al.* (August 24, 2008) Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. *Nature Neurosci*, 10.1038/nn.2177.
9. Oakson G, Steriade M (1982) Slow rhythmic rate fluctuations of cat midbrain reticular neurons in synchronized sleep and waking. *Brain Res* 247:277–288.
10. Honey CJ, Kotter R, Breakspear M, Sporns O (2007) Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proc Natl Acad Sci USA* 104:10240–10245.
11. Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Rev* 8:700–711.
12. Hagmann P, *et al.* (2008) Mapping the structural core of human cerebral cortex. *PLoS Biol* 6:e159.
13. Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* 265:676–679.
14. Kudrimoti HS, Barnes CA, McNaughton BL (1999) Re-activation of hippocampal cell assemblies: Effects of behavioral state, experience, and EEG dynamics. *J Neurosci* 19:4090–4101.
15. Raichle ME, *et al.* (2001) A default mode of brain function. *Proc Natl Acad Sci USA* 98:676–682.
16. Attwell D, Laughlin SB (2001) An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab* 21:1133–1145.
17. Friston KJ (1997) Transients, metastability, and neuronal dynamics. *NeuroImage* 5:164–171.
18. Balduzzi D, Tononi G (2008) Integrated information in discrete dynamical systems: motivation and theoretical framework. *PLoS Comput Biol* 4:e1000091.
19. Fox MD, Snyder AZ, Vincent JL, Raichle ME (2007) Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron* 56:171–184.
20. Yuval-Greenberg S, Tomer O, Keren AS, Nelken I, Deouell LY (2008) Transient induced gamma-band response in EEG as a manifestation of miniature saccades. *Neuron* 58:429–441.