Spotlight

Cell PRESS

A BOLD statement about the hippocampal-neocortical dialogue

György Buzsáki and Adrien Peyrache

NYU Neuroscience Institute and Center for Neural Sciences, New York University, New York, NY 10016, USA

High speed and high spatial resolution are at the top of the wish list of every neuroscientist. An important step of progress in this direction has now been made by sampling throughout the brain fMRI signals that temporally surround important physiological patterns.

The wisdom that the combination of two methods is more than their sum is illustrated with 'grandeur' in a paper by Logothetis *et al.* published recently in Nature [1]. In it, the authors combined fast time-scale electrophysiological techniques with whole brain fMRI in anesthetized and awake monkeys at rest. The results provided a snapshot of the cooperative patterns of the large numbers of brain structures involved either leading to or responding to a specific physiological event, the so-called hippocampal sharp wave-ripple (SPW-R). Beyond the specific theoretical question the paper addresses, the combined method used, which the authors call 'neural-event-triggered functional magnetic resonance or NET-fMRI', provides a new method for examining the spatial embeddedness of *a priori* defined local brain patterns.

The idea behind this study is simple: the authors selected an electrophysiologically well-characterized brain pattern as a seed and examined the metabolic state of nearly the entire brain surrounding that event (Figure 1). In practice, multiple difficult engineering problems had to be solved in order to achieve that goal, especially the elimination of the large electromagnetic fields that can interfere with the recordings of small amplitude local field potentials. In addition, the authors developed an MRI-assisted method to precisely place their probes within and across the CA1 pyramidal layer of the hippocampus. Both of these innovations stand as testimony of the technical brilliance characteristic of this laboratory.

After solving the technical issues, the authors focused on a long-standing scientific question, namely, the ability of the hippocampus to reach broad areas of the brain during its self-generated SPW-R activity. SPW-R activity exhibits the most synchronous physiological patterns in the mammalian brain and recruits tens of thousands of neurons in the hippocampus-entorhinal axis [2]. Their selective erasure interferes with memory consolidation [3], presumably because SPW-Rs represent the key communication link between hippocampal output and the neocortex [4,5]. The timing and possibly the spike content of SPW-Rs can be phase-modulated by sleep spindles (12-18 Hz) [6], both patterns are biased by slow oscillations (0.5-1.5 Hz), and the occurrence of the three rhythms is temporally coordinated by the ultraslow oscillation (0.1 Hz) [7]. The presence of multiple time scales and cross-frequency coupling mechanisms involved in shaping hippocampal SPW-R events indicates that complex, large-scale neuronal machinery is dedicated to the information exchange between the neocortex and hippocampus.

Although it has been known that SPW-Rs can affect firing patterns in both neocortical and subcortical structures, previous recordings involved only one or a few structures that 'partnered' with the hippocampus. By contrast, Logothetis and colleagues now supply an exhaustive list of cortical and subcortical structures that can be affected by or may contribute to the emergence of hippocampal SPW-Rs. The list is interesting: nearly all neocortical areas, with the exception of the visual cortex, show an increase in BOLD activity in association with SPW-Rs, whereas the thalamus and numerous other subcortical structures display a decrease in BOLD. The authors hypothesize that SPW-Rs represent special and privileged temporal windows when suppression of the subcortical inputs transiently enables strong hippocampal-neocortical communication and, at the same time, suppression of thalamocortical neurons prevents sensory inputs from interfering with the internal 'business' of the brain.

As is the case with all exciting results, the novel findings of Logothetis and colleagues raise as many questions as they answer. Perhaps the most important one is the recurring issue regarding the relationship between neuronal synaptic and spiking activity, on the one hand, and the physiological meaning of the BOLD signal, on the other. In what sense does the decreased BOLD signal reflect neuronal disengagement or suppression of activity? Does the decrease imply that the thalamus and other subcortical areas are not involved at all in the yin-yang of slow oscillations and sleep spindles, which are coupled (albeit weakly) to SPW-Rs? This would be an unexpected outcome, given ample physiological evidence that neurons in both the thalamus [8] and the basal forebrain [9] fire prominently during such events. One potential answer is that neurons in subcortical structures fire in short duty cycles, thus their overall metabolic costs actually decrease during oscillations, whereas persistent firing in the neocortex would be responsible for the increased BOLD [10]. However, this explanation is not fully consistent with the authors' observation that during hippocampal gamma episodes BOLD activity in all studied areas was positively correlated. Thus, the special mechanisms involved in SPW-R events need to be explored further. Unfortunately, given the physiological speed of neuronal communication, the cause-effect relationships are hard to decipher with

Corresponding author: Buzsáki, G. (Gyorgy.Buzsaki@nyumc.org).

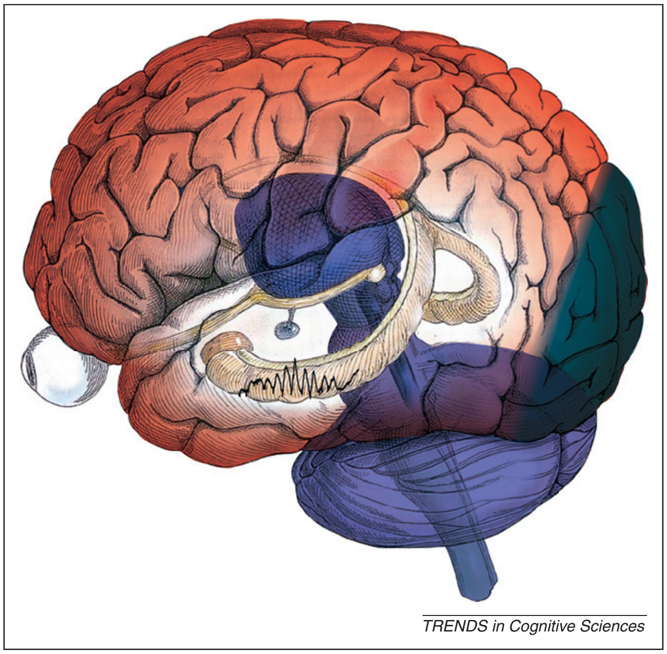

Figure 1. Hippocampal-neocortical interaction. Self-generated, synchronous sharp wave ripples (SPW-R) enhance and suppress BOLD activity in neocortical and subcortical areas, respectively. Such a gating mechanism may help to maintain hippocampus-dependent and procedural memories distinct and prevent sensory inputs from influencing memory consolidation.

certainty with the resolution at the scale of seconds of the NET-fMRI method. A further consideration is that SPW-Rs are not synchronous along the entire septo-temporal axis of the hippocampus, but, in fact, can be largely independent at the septal (tail) and temporal (uncal) poles. Therefore, it would be of great interest to know if SPW-Rs from the two poles can entrain overlapping or distinct brain areas.

Numerous other exciting questions can now be addressed using the NET-fMRI approach introduced by Logothetis and colleagues, including how slow oscillations, sleep spindles, theta rhythms, and other events are embedded in larger networks. We can hardly wait for the answers.

References

1 Logothetis, N.K. *et al.* (2012) Hippocampal-cortical interaction during periods of subcortical silence. *Nature* 491, 547–553

2 Chrobak, J. and Buzsaki, G. (1994) Selective activation of deep layer (V-VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat. *J. Neurosci.* 14, 6160–6170

3 Girardeau, G. *et al.* (2009) Selective suppression of hippocampal ripples impairs spatial memory. *Nat. Neurosci.* 12, 1222–1223

4 Buzsaki, G. (1989) Two-stage model of memory trace formation: a role for 'noisy' brain states. *Neuroscience* 31, 551–570

5 Carr, M.F. *et al.* (2011) Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nat. Neurosci.* 14, 147–153

6 Siapas, A.G. and Wilson, M.A. (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron* 21, 1123–1128

7 Sirota, A. *et al.* (2003) Communication between neocortex and hippocampus during sleep in rodents. *Proc. Natl. Acad. Sci. U.S.A.* 100, 2065–2069

8 Steriade, M. *et al.* (1993) The slow ($<$ 1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. *J. Neurosci.* 13, 3284–3299

9 Détári, L. *et al.* (1999) The role of basal forebrain neurons in tonic and phasic activation of the cerebral cortex. *Prog. Neurobiol.* 58, 249–277

10 Dang-Vu, T.T. *et al.* (2008) Spontaneous neural activity during human slow wave sleep. *Proc. Natl. Acad. Sci. U.S.A.* 105, 15160

http://dx.doi.org/10.1016/j.tics.2012.12.009 Trends in Cognitive Sciences xx (2013) 1–2