Cell PRESS

The fMRI signal, slow cortical potential and consciousness

Biyu J. He and Marcus E. Raichle

Mallinckrodt Institute of Radiology, Washington University School of Medicine, 4525 Scott Avenue, St. Louis, MO 63110, USA

As functional magnetic resonance imaging (fMRI) has become a driving force in cognitive neuroscience, it is crucial to understand the neural basis of the fMRI signal. Here, we discuss a novel neurophysiological correlate of the fMRI signal, the slow cortical potential (SCP), which also seems to modulate the power of higher-frequency activity, the more established neurophysiological correlate of the fMRI signal. We further propose a hypothesis for the involvement of the SCP in the emergence of consciousness, and review existing data that lend support to our proposal. This hypothesis, unlike several previous theories of consciousness, is firmly rooted in physiology and as such is entirely amenable to empirical testing.

Introduction

Since its introduction in the early 1990s, functional magnetic resonance imaging (fMRI) has become the most widely used tool in human cognitive neuroscience and has produced a formidable array of brain maps depicting both localization (as in traditional activation studies) and integration (as in more recent functional connectivity studies) of brain activity. Because the fMRI signal measures directly blood oxygenation and only indirectly neuronal activity, an important need for understanding the neural events contributing to the fMRI signal has been widely recognized. Such a need is further stressed by the inconsistencies between several human fMRI and monkey unit physiological studies employing the same tasks [1].

Responding to this need, several studies have compared the fMRI signal (reviewed in Ref. [2]) or its close relatives (including tissue oxygenation [3], blood flow [4] and optical intrinsic signals [5]) with simultaneously recorded electrophysiological signals. The convergent results from these studies suggest that the fMRI signal is contributed predominantly by synaptic activity representing inputs and local processing in an area as measured by local field potentials (LFP) [2–4,6,7]. The spiking activity, though often correlated with both the LFP and the fMRI signal, can be dissociated from the latter two in several conditions, including adaptation [8], drug modulation [9], manipulations of excitatory and inhibitory inputs [4] and a spatial separation between input and output activity [7].

Whereas multiple frequency ranges of the LFP (e.g. 5–30 Hz [10], 20–60 Hz [11,12], ~25–90 Hz [3,5,8,9,13]) have been correlated with the fMRI signal in different conditions, all of these studies have only assessed power modulations of the LFP because only the power of these frequency ranges has a comparable temporal scale to that of the fMRI signal (< 0.5 Hz). Here, we add a new dimension to this evolving story by bringing in the low-frequency end of field potentials (<4 Hz), which, with a temporal scale overlapping that of the fMRI signal, seems to correlate with the fMRI signal in its raw fluctuations. This signal, termed the 'slow cortical potential' (SCP) by us and others [14–16], seems optimally positioned for carrying out large-scale information integration in the brain. Because conscious experience* is always a unitary and undivided whole [17,18], segregated information processing in the brain cannot contribute to the conscious awareness of 'I'. Hence, we propose that the SCP might contribute directly to the emergence of consciousness and review existing empirical evidence supporting this idea. As the current hypothesis is based on a well-defined, well-characterized physiological process, it is entirely amenable to empirical testing.

Evidence for a relationship between the SCP and the fMRI signal

The SCP is the slow end (mainly <1 Hz, can extend up to ~4 Hz) of the field potential that can be recorded using either depth [19,20] or surface [15,21] electrodes (Box 1). Negative shift in surface-recorded SCP indexes increased cortical excitability (for detailed physiology please see the following section). Because the SCP frequency range is subject to artifacts due to sweating (in scalp-electroencephalography [EEG] recordings), movement and electrode drift (if polarizable electrodes are used), it has been eliminated in most animal physiology and human EEG studies by online high-pass filtering. This is unfortunate because, as was recognized in the 1970s, 'If DC [i.e. direct-current] recording is used, virtually every stimulus-bound cortical activity is seen to be accompanied by a change in cortical steady potentials' [19]. As a result of this methodological neglect, studies on the relationship between SCP and the fMRI signal are scarce. Nonetheless, despite the limited data available, a correlation between the SCP and the fMRI signal, no less intimate than that between higher-frequency (>5 Hz) LFP power and fMRI signal, can be observed [15,16,22].

Investigations of the relationship between LFP power and the fMRI signal have usually showed one of the

Corresponding author: He, B.J. (biyu.jade.he@gmail.com)

* In this article, we use 'consciousness' or 'conscious awareness' synonymously as 'subjective awareness'. We use 'conscious experience' to refer to the experience of subjective awareness. Lastly, 'conscious state' refers to the physiological states under which conscious awareness is present..

1364-6613/$ – see front matter doi:10.1016/j.tics.2009.04.004 Available online 15 June 2009

Box 1. Is the SCP an oscillation?

The SCP frequency band has also been referred to as 'infraslow oscillations' [37], but is the SCP really an oscillation? EEG can be classified in three distinct groups [1]: rhythmic, arrhythmic and dysrhythmic. The first two appear in normal subjects and refer to waves of approximately constant frequency and no stable rhythms, respectively. The latter refers to pathological rhythms in patient groups. Rhythmic EEG is further subdivided into frequency bands known as δ, θ, α, β and γ, etc. The SCP frequency range does not normally contain any true rhythmic activity, except the 'up-and-down states' (also called the 'slow oscillation' by its discoverer [71]) that occurs during deep sleep (~0.8 Hz). The 'up-and-down states' is a distinct phenomenon that can be easily differentiated from the SCP (for detailed discussions see supplementary materials in He *et al.* [15]). Therefore SCP is a fluctuation rather than oscillation [72] (B.J. He *et al.*, unpublished). The confusion between fluctuations and oscillations, or, arrhythmic and rhythmic activities, is quite common. This is largely because time-frequency analyses widely adopted create artificial rhythmic signals. However, as pointed out by T.H. Bullock [48], 'Most of the time in most animals there is little evidence of really rhythmic oscillators in the ongoing cerebral activity, let alone that rhythms account for much of the total energy'. We here avoid using terms such as 'delta' or 'infra-delta' to describe the SCP because these terms have connotations of oscillations that are not present in an arrhythmic signal.

following: (i) covariation of simultaneously recorded LFP power and the fMRI signal during a task or electrical stimulation [3,5,8,9,11,12], (ii) covariation of simultaneously recorded spontaneous LFP power and the fMRI signal [23] and (iii), similar correlation patterns in the spontaneous fluctuations of LFP power and the fMRI signal measured separately [15,24,25].

To our knowledge, the only available data that demonstrate covariation of simultaneously recorded SCP and the fMRI signal during task stimulation [akin to aforementioned type (i)] has been provided by Nagai and colleagues [22] using simultaneously recorded EEG and fMRI. These authors found a trial-by-trial correlation between the amplitude of a negative SCP response indexing expectancy ('contingent negative variation' [CNV]) and the fMRI signal amplitude in anterior cingulate cortex (Figure 1a). The anterior cingulate has previously been determined as a generator region of CNV [22]. Evidence for SCP–fMRI correlation of the aforementioned type (ii) is provided by Jones *et al.* [26], who showed that spontaneously fluctuating total hemoglobin concentration (a signal tightly linked to the fMRI signal) and low-pass filtered LFP (i.e. depth recorded SCP) are temporally correlated. Data of the aforementioned type (iii) is provided by He *et al.* using invasive EEG (i.e. electrocorticography, ECoG) and fMRI in neurosurgical patients [15]. It was shown that large-scale (2–10 cm on cortical surface) correlation patterns in the spontaneous SCP and fMRI signals were similar (Figure 1b). This finding has since been extended to inter-hemispheric correlations as well (B.J. He *et al.*,unpublished). Taken together, all three types of evidence for the correlation between LFP power and the fMRI signal are also available for a correlation between SCP and the fMRI signal.

Beyond these approaches, there is an extensive literature showing similar modulation patterns of the SCP and the fMRI signal in a wide range of cognitive tasks [14,16,21]. For example, visual working memory tasks elicit a negative-going slow potential over the parietal cortex, the amplitude of which scales with the load of working memory [27]. This pattern is very similar to that observed for the fMRI signal in posterior parietal cortex during the same task [28].

In summary, convergent results suggest that the SCP has a close correspondence to the fMRI signal in different experimental conditions. Like many advances in science, the relationship between SCP and fMRI signal is not without prescient conjecture. In 1975, H.W. Shipton wrote: 'the work of Cooper, which showed slow rhythmic changes in brain pO_2 and in blood flow (e.g. [29]), is of interest in the

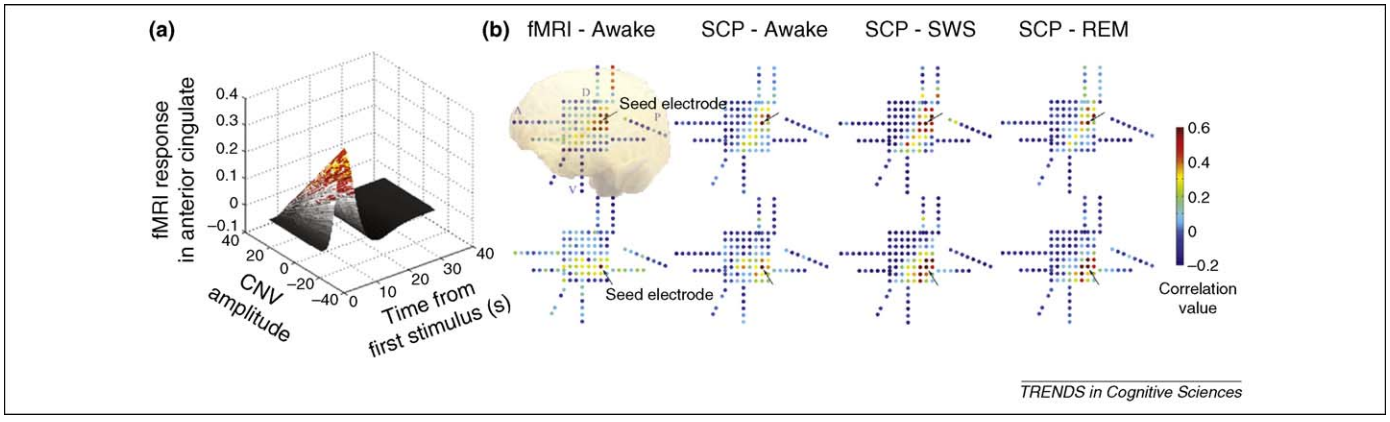

Figure 1. Evidence for a correlation between the slow cortical potential (SCP) and the fMRI signal. **(a)** Simultaneous fMRI and EEG was used to identify fMRI signal activation correlated with trial-by-trial measurement of contingent negative variation (CNV) amplitude. CNV is a negative slow potential that relates to the anticipation of a stimulus and it is maximal over frontal midline electrodes. Trial-by-trial covariation between CNV amplitude and fMRI signal time course in anterior cingulate cortex is shown in a 3D plot. Adapted with permission, from Nagai *et al.* [22] **(b)** Correlation patterns in the spontaneous fMRI signals and spontaneous SCPs are similar. A group of 5 patients with intractable epilepsy underwent approximately a week of continuous video-monitored electrocorticography (ECoG) for the purpose of determining the epileptic focus before surgical resection. Artifact-free, spontaneous ECoG data were collected from three arousal states: wakefulness, slow-wave sleep (SWS) and rapid-eye-movement (REM) sleep, and then low-pass filtered at <0.5 Hz to yield spontaneous SCPs. In addition, patients underwent a session of resting-state fMRI before or after surgical intervention. SCP correlation maps were obtained by computing Pearson correlation coefficients between a seed electrode (arrow) and all other electrodes. For corresponding fMRI correlation maps, the fMRI signal was averaged across a group of voxels centered at each electrode, and correlation coefficients were computed between the fMRI signal associated with the seed electrode and that from all other electrodes. Representative maps from one patient are shown. A 2D representation of the electrode grid is shown with each dot representing one electrode. Color represents the correlation value between each electrode and the seed electrode (arrow). Maps in the top row seed at a same electrode, those in the bottom row seed at another electrode 2 cm apart. Note that correlation maps with the same seed electrode are similar regardless of whether the fMRI signal or the SCP was used in computing the map. Abbreviations: A, anterior; D, dorsal; P, posterior; V, ventral. Adapted, with permission, from He *et al.* [15]