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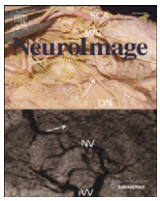

Spatiotemporal dynamics of the brain at rest — Exploring EEG microstates as electrophysiological signatures of BOLD resting state networks

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ABSTRACT

Neuroimaging research suggests that the resting cerebral physiology is characterized by complex patterns of neuronal activity in widely distributed functional networks. As studied using functional magnetic resonance imaging (fMRI) of the blood-oxygenation-level dependent (BOLD) signal, the resting brain activity is associated with slowly fluctuating hemodynamic signals (~10 s). More recently, multimodal functional imaging studies involving simultaneous acquisition of BOLD-fMRI and electroencephalography (EEG) data have suggested that the relatively slow hemodynamic fluctuations of some resting state networks (RSNs) evinced in the BOLD data are related to much faster (~100 ms) transient brain states reflected in EEG signals, that are referred to as "microstates".

To further elucidate the relationship between microstates and RSNs, we developed a fully data-driven approach that combines information from simultaneously recorded, high-density EEG and BOLD-fMRI data. Using independent component analysis (ICA) of the combined EEG and fMRI data, we identified thirteen microstates and ten RSNs that are organized independently in their temporal and spatial characteristics, respectively. We hypothesized that the intrinsic brain networks that are active at rest would be reflected in both the EEG data and the fMRI data. To test this hypothesis, the rapid fluctuations associated with each microstate were correlated with the BOLD-fMRI signal associated with each RSN.

We found that each RSN was characterized further by a specific electrophysiological signature involving from one to a combination of several microstates. Moreover, by comparing the time course of EEG microstates to that of the whole-brain BOLD signal, on a multi-subject group level, we unraveled for the first time a set of microstate-associated networks that correspond to a range of previously described RSNs, including visual, sensorimotor, auditory, attention, frontal, visceromotor and default mode networks. These results extend our understanding of the electrophysiological signature of BOLD RSNs and demonstrate the intrinsic connection between the fast neuronal activity and slow hemodynamic fluctuations.

Introduction

The activity of the resting brain, as measured using blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI), reveals spontaneous, large-amplitude, low-frequency (<0.1 Hz) fluctuations that are temporally correlated and spatially organized into specific functional networks, collectively termed the "resting state networks" (RSNs) (Biswal et al., 1995; Fox and Raichle, 2007). Multiple RSNs can be identified using seed-based correlation mapping to activity measured over spatial loci selected a priori (Biswal et al., 1995), or can be delineated using data-driven approaches, such as independent component analysis (ICA) (Beckmann et al., 2005; Calhoun et al., 2001; Damoiseaux et al., 2006; Mantini et al., 2007). The RSNs are evident in the human brain during the awake resting state, as well as during task performance, sleep and anesthesia (Fox and Raichle, 2007), or at different vigilance level (Olbrich et al., 2009). In experimental animals RSNs also have been demonstrated under anesthesia (Vincent et al., 2007) and wakeful rest (Liang et al., 2011). Each RSN resembles either the spatial pattern of BOLD responses elicited by active behavioral tasks involving the task-relevant visual, sensorimotor, auditory, or attentional modality (Smith et al., 2009), or by the spatial network of regions that are active in a resting state but decrease activity in most tasks (i.e., the "default" mode network) (Greicius et al., 2003; Raichle et al., 2001). More recent evidence suggests that spontaneous brain activity plays an important role in regulating behavioral responses by providing endogenous or top-down modulation of sensory or cognitive processing (Boly et al., 2007; Hesselmann et al., 2008). Meanwhile, emerging evidence shows that neurological or psychiatric diseases are associated with alterations in RSN activity (Fornito and Bullmore, 2010). Thus, the spontaneous BOLD activity of RSNs reflects a fundamental aspect of cerebral physiology.

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The neurophysiological basis of the BOLD RSNs is not fully understood, however. The BOLD signal is an indirect measure of neural activity (Logothetis, 2008), and the extent to which slow fluctuations of RSNs at the level of ~10 s reflect faster neuronal dynamics at the millisecond level remains unclear. If indeed BOLD RSNs are linked to fast neuronal activity it is also not clear what are physiological relevant mechanisms establishing such link. Although substantial evidence links task-evoked BOLD responses to spiking activity (Logothetis et al., 2001), local field potentials (Logothetis et al., 2001; Mukamel et al., 2005), and macro-level recording (such as electroencephalography, EEG) (Yuan et al., 2011), the electrophysiological correlates of spontaneous BOLD activity in the RSNs have not been established. A seminal finding in this regard, however, was the report that slow fluctuations (also <0.1 Hz) of band-limited power measured invasively using intracranial electrodes were correlated between brain areas within (He et al., 2008; Leopold et al., 2003) and across hemispheres (Nir et al., 2008). Moreover, to investigate potential links between spontaneous neural electrophysiological activity and BOLD fluctuations, several studies simultaneously measured EEG and BOLD-fMRI signals to assess band-limited EEG power as electrophysiological correlates for RSNs. The EEG power in the alpha (8–13 Hz) or beta (13–30 Hz) frequency band was correlated with the spontaneous BOLD signal in brain regions that partially overlap with some RSNs, particularly in the visual/parietal cortex (Goldman et al., 2002; Laufs et al., 2003; Moosmann et al., 2003; Sadaghiani et al., 2010). Another concurrent EEG and BOLD fMRI study correlated the time course of six RSNs with the time course of EEG power across a wide spectrum of frequency bands (1–50 Hz) (Mantini et al., 2007). A diverse electrophysiological profile was obtained for these six RSNs that showed each RSN was correlated with EEG activity at all frequency bands; however, signatures specific to each RSN were not identified. Spontaneous electrophysiological activity as reflected by EEG does not generally exhibit a single frequency or even single frequency band oscillations, and instead a wide spectrum of rhythms generally is collectively represented in the EEG signal (Buzsaki and Draguhn, 2004; Varela et al., 2001). The neural activity at a specific frequency band thus is unlikely to constitute the electrophysiological correlate of an RSN.

Recently, microstates of the EEG signal have been proposed as potential electrophysiological correlates of spontaneous BOLD activity (Britz et al., 2010; Musso et al., 2010). The topographic representation of the EEG scalp electrical field affords temporal resolution at the millisecond-level, yet does not change randomly or continuously over time, remaining stable over periods of ~100 ms. Such quasi-stable and unique topographic distributions of the electrical field potential have been termed "microstates" (Lehmann, 1980; Lehmann, 1990; Lehmann et al., 1987). The EEG microstate reflects the summation of concomitant neuronal activity across brain regions rather than activity specific to any frequency band (Koenig et al., 2002; Lehmann, 1980; Lehmann et al., 1987; Wackermann et al., 1993). Microstates in spontaneous activity have been associated with abstract thoughts arising as subjects rest in an awake state (Lehmann et al., 1998) and the pre-stimulus states also have been shown to influence the subsequent task-evoked BOLD response (Arieli et al., 1996; Britz et al., 2009). Moreover, EEG microstate analysis was used to differentiate subjects with panic disorders from healthy controls (Kikuchi et al., 2011), suggesting potential applications in psychiatric research.

Two previous studies used concurrent EEG and BOLD-fMRI to investigate the correlation between microstates and spontaneous BOLD activity (Britz et al., 2010; Musso et al., 2010). In both studies microstates were segregated into multiple groups based upon the maximum spatial dissimilarity between groups. A microstate time course was derived using the spatial correlation between instantaneous topography and each group, and then compared to the BOLD signal over entire brain using a general linear model approach. Specific brain regions in which the BOLD activity correlated to the microstate time courses also were identified, and these regions appeared to partially overlap with known RSNs, suggesting that microstates may serve as informative electrophysiological correlates of the spontaneous BOLD activity. However, in both studies the spatial similarity was the key factor used to ascribe microstates to different groups and to determine the time course of each microstate, irrespective of the temporal information contained in the EEG recording. Therefore, the topographies on the scalp associated with microstates originating from distinct brain areas could have been partially correlated due to the volume conduction effect (Nunez, 1995), and yet could have been ascribed into the same group. Moreover, the spatial dissimilarity between groups did not guarantee temporal independence (e.g., microstates 1 and 2 in Britz et al., 2010 were strongly correlated). Thus, when comparing the time course of microstates to that of the BOLD signal, partially correlated microstates would eliminate the independence across networks, resulting in overlap between the networks associated with various microstates.

In order to overcome this limitation, and to investigate the extent to which the BOLD RSNs reflect neuronal activity, we developed a novel, data-driven approach to extract the microstates in EEG using independent component analysis (ICA). We applied ICA to decompose the EEG recording into thirteen spatially distinct microstates that showed maximal temporal independence from each other. In the meantime, ten RSNs were identified from simultaneously collected BOLD fMRI data using spatial ICA. We hypothesized that the intrinsic RSNs would be reflected in EEG activity as well as in BOLD activity. To test this hypothesis, we examined the temporal correlation between the independent microstates and BOLD activity within RSNs. Each RSN was characterized by a specific electrophysiological signature involving one, two, or a combination of several, microstates. To further examine the spatial specificity of temporal independent microstates with respect to their relationship to a particular RSN, the time courses of the microstates were compared to that of the whole-brain BOLD signal in a general linear model and, for the first time, electrophysiological correlates were found for a wide range of networks, including the canonical visual, motor, auditory, attention, frontal, visceromotor and default mode networks.

Material and methods

Subjects and experimental protocol

The study was conducted at the Laureate Institute for Brain Research, and was approved by the University of Oklahoma Institutional Review Board (IRB). Nine healthy, right-handed subjects (mean age = 33 ± 10 years; one female) participated in the study. All participants provided written informed consent as approved by the University of Oklahoma IRB. The subjects received financial compensation for their participation.

Simultaneous EEG and fMRI data were recorded on each subject over three functional imaging sessions, each lasting 6 min and 10 s. Subjects were instructed to rest with eyes closed and to remain awake. Upon debriefing none of the subjects reported sleeping during the study sessions and subsequent inspection of the EEG confirmed the self-reports. The data from all nine subjects (27 functional sessions in total) were included in the analysis.

Simultaneous EEG/fMRI recording

High-density EEG signals from 126 channels were recorded using MRI-compatible BrainAmp MR Plus amplifiers (Brain Products GmbH, Munich, Germany). The sintered Ag/AgCl ring electrodes were mounted into a scalp cap according to the standard 10–5 system. All electrodes were referenced to the FCz position, while a ground electrode was located at the AFz position. One additional electrode was placed on the subjects' back to monitor the electrocardiographic