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Hemodynamic and electrophysiological spontaneous low-frequency oscillations in the cortex: Directional influences revealed by Granger causality

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ABSTRACT

We used a combined electrophysiological/hemodynamic system to examine low-frequency oscillations (LFOs) in spontaneous neuronal activities (spike trains and local field potentials) and hemodynamic signals (cerebral blood flow) recorded from the anesthetized rat somatosensory and visual cortices. The laser Doppler flowmetry (LDF) probe was tilted slightly to approach the area in which a microelectrode array (MEA) was implanted for simultaneous recordings. Spike trains (STs) were converted into continuous-time rate functions (CRFs) using the ST instantaneous firing rates. LFOs were detected for all three of the components using the multi-taper method (MTM). The frequencies of these LFOs ranged from 0.052 to 0.167 Hz (mean ± SD, 0.10 ± 0.026 Hz) for cerebral blood flow (CBF), from 0.027 to 0.26 Hz (mean ± SD, 0.12 ± 0.041 Hz) for the CRFs of the STs and from 0.04 to 0.19 Hz (mean ± SD, 0.11 ± 0.035 Hz) for local field potentials (LFPs). We evaluated the Granger causal relationships of spontaneous LFOs among CBF, LFPs and CRFs using Granger causality (GC) analysis. Significant Granger causal relationships were observed from LFPs to CBF, from STs to CBF and from LFPs to STs at approximately 0.1 Hz. The present results indicate that spontaneous LFOs exist not only in hemodynamic components but also in neuronal activities of the rat cortex. To the best of our knowledge, the present study is the first to identify Granger causal influences among CBF, LFPs and STs and show that spontaneous LFOs carry important Granger causal influences from neural activities to hemodynamic signals.

Introduction

During the past half-century, spontaneous low-frequency oscillations (LFOs) have generally been considered to be physiological noise and have been minimized (Fox and Raichle, 2007; Gilden et al., 1995; Palva and Palva, 2012; Wise et al., 2004). However, an increasing number of studies have revealed that spontaneous LFOs are not random noise but exhibit stable patterns, even in task-based research (Fox et al., 2007; Kannurpatti et al., 2008; Leopold et al., 2003). These oscillations can be of equal magnitude to (Nir et al., 2006) or even an order of magnitude greater than (Mayhew et al., 1996) brain responses to exogenous stimuli. Spontaneous LFOs are currently related to a wide variety of brain-generated functions (Buzsaki, 2006) and are able to coordinate gross cortical excitability and synchronize various operations across neuronal networks (Balduzzi et al., 2008; Buzsaki and Draguhn, 2004; Vanhatalo et al., 2004; Varela et al., 2001). This coordination or synchronization is required for global and collective decisions, which are associated with most cortical functions (Buzsaki, 2006), such as alertness and vigilance (He, 2003; Xu et al., 2007), recording and memory (Burke et al., 2013; Foster and Willson, 2006; Kenet et al., 2003) and dynamic prediction (Buzsaki and Draguhn, 2004; Pouget et al., 2003). When LFOs are compromised, individuals may be treated for diseases, including schizophrenia (Hoptman et al., 2010), Alzheimer's disease (AD) (Damoiseaux et al., 2008), multiple sclerosis (Lowe et al., 2002), major depression (Anand et al., 2005), attention deficit-hyperactivity disorder (ADHD) (Castellanos and Margulies, 2008) and autism (Kennedy and Courchesne, 2008). Consequently, it is worthwhile to examine signals in the low-frequency range to explore particular brain functions and the etiology of psychiatric diseases.

Spontaneous LFOs have been widely examined in the context of hemodynamic parameters; these spontaneous activities are referred to as "Mayer waves," "V-signals" or "0.1 Hz oscillations" (Mayhew et al., 1996; Obrig et al., 2000). The existence of an approximately 0.1 Hz oscillation in cerebral blood flow (CBF) has been widely recorded using laser Doppler flowmetry (LDF) (Hudetz et al., 1992; Morita-Tsuzuki et al., 1992). Mayhew et al. (1996) reported a pervasive "0.1 Hz oscillation" in intrinsic cortical signals recorded using optical imaging (OI). This low-frequency component was very similar to the oscillations that were measured concurrently in the CBF using LDF. Using functional magnetic resonance imaging (fMRI), Biswal et al. (1995) observed correlative spontaneous LFOs (<0.08 Hz) in the human left and right

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somatosensory cortices from blood oxygenation level-dependent (BOLD) signals; these LFOs were similar and coupled to CBF (Attwell and Iadecola, 2002; Ekstrom, 2010; Kannurpatti et al., 2008). This seminal finding of spontaneous LFOs has since been supported by several studies (Fox et al., 2007; Kannurpatti et al., 2008; Lowe et al., 1998; Nir et al., 2006). Cordes et al. (2001) reported that regionally specific BOLD correlations were predominantly (85–90%) from low-range (<0.1 Hz) contributions; therefore, the majority of spontaneous BOLD studies have applied low-pass filters with a cut-off of 0.08 or 0.1 Hz to the data (Fox and Raichle, 2007; Majeed et al., 2011). In fact, most resting-state fMRI studies have focused on mapping the spatial distribution of temporal correlations between spontaneous LFOs, studying what is commonly referred to as "resting-state functional connectivity" (RSFC) (Friston et al., 1993; Zuo et al., 2010). Eight functionally linked subnetworks, known as "resting-state networks" (RSN), have been reproducibly identified with a high level of RSFC (Doucet et al., 2012; van den Heuvel and Hulshoff Pol, 2010). Recent studies based on RSFC and RSN have reported that LFOs in patients with psychiatric diseases are unlike those observed in healthy controls, with multiple brain regions exhibiting either increases or decreases in amplitude and spatial coherence (Auer, 2008).

However, the mechanism that induces spontaneous LFOs in hemodynamics remains unclear (Fox and Raichle, 2007; Kannurpatti et al., 2008; Kim and Ogawa, 2012). Due to its complexity, the precise etiology of many LFO-related diseases is unknown (Auer, 2008; Cheng et al., 2012). The neuronal basis of RSFC is also incompletely understood (Sirotin and Das, 2009; van den Heuvel and Hulshoff Pol, 2010). Ekstrom (2010) suggested a mixture of hope and caution regarding how effectively the BOLD signal can be used as a proxy for underlying neural activity. Although helpful fMRI studies of LFOs are increasing, the link between the propagation of BOLD signals and that of neural activities, which is important for interpreting fMRI signals (Arthurs and Boniface, 2002; Ekstrom, 2010), has yet to be established (Majeed et al., 2011; Zuo et al., 2010). Until now, the potential origin of hemodynamic LFOs has been believed to be metabolic, myogenic or neurogenic (Cheng et al., 2012). Early studies that measured spontaneous LFOs in cytochrome oxidase activity under conditions of electrocortical silence supported the metabolic mechanism (Vern et al., 1988), but this view was found to be untenable based on the results of an fMRI study (Attwell and Iadecola, 2002). Researchers have suggested that hemodynamic LFOs are myogenic-dependent (Morita-Tsuzuki et al., 1995). Mathematical models using a myogenic mechanism demonstrated that vasomotion oscillations can be propagated locally and are self-sustained within certain limits; however, the models presented were clearly simplifications of the underlying mechanisms (Ances et al., 2010; Behzadi and Liu, 2005). Evidence is mounting that neural activity is the primary contributor to spontaneous LFOs. Golanov et al. proposed that LFOs are neurogenic (Golanov et al., 1994). Slow neuronal oscillations between 0.1 and 1 Hz have been previously reported, and the neocortex has been shown to be the main structure responsible for the generation of these oscillations (Steriade et al., 1993a,b,c). He (2003) demonstrated the existence of low-frequency (0.03 to 0.25 Hz) spike trains (STs) in auditory thalamus neurons in anesthetized guinea pigs. Because the thalamic slow oscillation could be terminated by cortical activation, He believed that the slow oscillation was initiated by the cortex. Vanhatalo et al. (2004) observed large-scale LFOs (0.02 to 0.2 Hz) in widespread human cortical regions using direct-current electroencephalography (EEG). Leopold and Logothetis' pioneering work on the neurophysiology of spontaneous LFOs utilized electrophysiological recordings in the visual cortex of monkeys. Large-amplitude LFOs were observed in LFP power fluctuations and exhibited a high correlation between electrode pairs. These authors proposed that LFPs may contribute substantially to LFOs measured using fMRI (Leopold et al., 2003). Subsequently, significant correlations were found between spontaneous LFOs in neural activities and those in hemodynamic signals in both animals and humans (Goncalves et al., 2006; He et al., 2008; Lu et al., 2007; Mukamel et al., 2005; Picchionia et al., 2011; Shmuel and Leopold, 2008). Nevertheless, correlation does not imply causation (Buzsaki, 2006). We have found no previous report that directly establishes a Granger causal relationship between LFOs in hemodynamics and LFOs in neural activities.

In the present study, we recorded spontaneous LFOs from the rat somatosensory and visual cortices using a combined LDF/MEA system in which three types of resting-state signals were simultaneously obtained. CBF from LDF recordings corresponded to the variables for hemodynamics, and STs and LFPs from MEA recordings corresponded to those for neural activities. Spontaneous LFOs were clearly detected in three types of recordings by spectral analysis. We then utilized the Granger causality (GC) model to extract Granger causal relationships between STs, LFPs and CBF. Significant Granger causal influences were observed from LFPs to CBF, from STs to CBF and from LFPs to STs at the low frequency. These results demonstrate that spontaneous LFOs exist not only in hemodynamic parameters but also in electrical neuronal activities from the rat cortex. To our knowledge, these results are the first to demonstrate that spontaneous LFOs carry Granger causal influences from neural activities to hemodynamic signals in the rat cortex.

Materials and methods

Animal preparation

Twelve male adult Sprague–Dawley (SD) rats (weighing 220 to 300 g) were provided by the Neurophysiology Department at Xiangya Medical College of Center South University. The rats were anesthetized with urethane (1.2 g/kg, 20%) by celiac injection prior to surgery. The animals were firmly mounted in a stereotaxic frame with two ear bars. A midline incision was made in the scalp. The skull and dura mater overlying the somatosensory or visual cortex were removed according to the stereotaxic rat brain atlas (Paxinos and Watson, 2007) to implant the MEA and place the LDF probe. We choose the somatosensory and visual cortices because these two regions were both large and sufficiently flat to implant the MEA and simultaneously emplace the LDF probe.

The animal's body temperature was maintained at 37.0 ± 0.5 °C using a feedback-controlled heating pad. The animal's respiration and heartbeat were monitored using a physiological recording instrument (MP150, BIOPAC Inc., Goleta, CA, USA). All of the surgical procedures were performed in accordance with the guiding principles for research involving animals and humans of Xiangya Medical College of Center South University.

Recording

The cortex of the rat was accessed vertically using a Tungsten MEA (2 × 8 channels, Gaithersburg, MD, USA). The MEA was connected with a Cerebus data acquisition system (Cyberkinetics Neurotechnology Systems, Inc.), which obtained the spike detection and data recording of STs and LFPs. When the electrodes (1 MΩ) were near or within the targeting area, the MEA was slowly advanced using a microdrive (2 μm/step). The depth of insertion was approximately 500 μm below the cortical surface given that layer IV of the cortex is believed to play a major role in neurovascular coupling and exhibits LFPs with the largest amplitude (Jones et al., 2004; Lautitzen, 2001; Nielsen and Lauritzen, 2001). When the electrophysiological recording device was ready, the small and lightweight probe of the LDF (LDF100C module of MP150) was carefully brought near the cortex to non-invasively monitor the regional microvascular blood supply in the tissue. Visual inspection of the cortical surface allowed for the large vessels to be avoided during LDF probe placement (Jones et al., 2004). The LDF probe was slightly tilted to enable observation of the area in which the MEA was implanted. This slight tilt was negligible, and we monitored the background signal of the probe to ensure the validity of the resulting recordings. In our

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