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The role of sub-second neural events in spontaneous brain activity

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Human fMRI studies have identified well-reproducible resting-state networks (RSN) from spontaneous recordings. These networks are extracted from correlation metrics across the brain using several minutes of data. However, a majority of electrophysiological events occur at a sub-second time scale and their contribution to RSN generation is likely. According to recent fMRI studies RSNs separate into smaller networks when studied with higher temporal resolution. Moreover, using simultaneous electrophysiology and fMRI recordings it was shown that transient functional networks form around neural events. Therefore, considering neural events as sources of functional networks might improve the understanding of spontaneous brain activity. This endeavor will benefit from technical advances in simultaneous BOLD and electrophysiology recordings, as well as a more principled modeling of neurovascular coupling.

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Introduction

Resting-state networks extracted with fMRI often show a remarkable correspondence to task-related functional networks [1]. These networks are obtained through temporal correlation of several minutes of recording from seeds across the brain or by spatially decomposing the data into independent components. However, when looking at the time scale of only a few seconds instead of minutes, these networks can be separated into smaller networks [2,3••]. Meanwhile, the actual neural processing in the brain is often in the time scale of tens of millisecond to sub-second range, with distinct events like spikes or ripples becoming apparent at this time scale. Evidence for the importance of these sub-second events for network generation has been provided by NK Logothetis *et al.* [4••]. During hippocampal ripples brain-wide networks are formed and can be detected from the BOLD signal. Yet, not much focus has been put on the possible contribution of such sub-second neural events for the generation of fMRI functional connectivity networks. In this review we present evidence for the importance of refining our understanding of spontaneous activity and network generation by combining time-averaged correlation studies with the analysis of neural events. We will first review current approaches to studying spontaneous activity with EEG, MEG, LFP, and fMRI and then point to recent findings which show the potential of analyzing event-based network generation using high-frequency time series. While all reported results are based on spontaneous activity, we will use the generic term ''network'' to denote the set of brain regions that is connected during rest as detected with any chosen imaging technique. In contrast, we will use the term ''resting-state network'' to denote the particular networks that are commonly found in the fMRI-based resting-state literature (which may or may not coincide with those detected with other techniques).

Measuring resting-state networks with different recording techniques

Currently, spontaneous activity and in particular resting-state networks are mainly studied with fMRI. The main advantages of fMRI are its high spatial resolution (up to 500 μm), the possibility to cover the whole brain, and its non-invasiveness. But fMRI only has a time resolution of around 1 s. Another issue is that fMRI measures the blood oxygen level (BOLD), which clearly reflects some aspects of neural activity, but the exact relationship underlying it is not yet clear [5,6]. Recent research has, for example, highlighted that the relation between neural and BOLD activity is heterogeneous across brain regions [7,8] and that the BOLD amplitude is not linearly related to the neural activity [9]. Thus, it is important for the interpretability of the BOLD signal in terms of neural activity to more thoroughly understand the sources of this variability.

This drawback can be partially mitigated by directly measuring neural activity non-invasively in humans with

Glossary

Gradient artefact: During the acquisition of MRI data, magnetic gradients are applied to obtain spatial information. These gradients are switched for every recording slice. This change in magnetic field induces artefacts in simultaneously acquired electrophysiological data. The artefacts are commonly several magnitudes larger than the actual electrophysiological data and therefore need to be removed.

Hemodynamic response: In response to neural activity, the blood flow within the active neural tissue increases to accommodate the higher oxygen and nutrient demand. This response of the blood flow and consequently increased oxygen levels due to neural activity is called the hemodynamic response. However, the exact relation between neural activity, blood flow, and oxygen consumption is still under investigation.

Hemodynamic response function: The statistical models used to represent the time course of the hemodynamic response after an initial event are called hemodynamic response functions. For example, the so-called canonical hemodynamic response function makes use of gamma functions.

Initial dip: Within the hemodynamic response, usually first a decrease in baseline oxygen level is seen before the hump-shaped increase materializes. This early signal change is attributed to the increased oxygen consumption immediately after the neural activation before the oxygen supply via increased blood flow within the neural tissue had time to materialize. Thus, the oxygen level initially undershoots.

Sigma wave: The frequency range from 11 to 15 Hz is referred to as the sigma band. Electrophysiological time series bursts within this frequency range occur in humans during stage 2 sleep and can be recorded with EEG. Sigma waves are also referred to as sleep spindles.

Sharp wave ripples: Sharp wave ripples occur within the hippocampus of immobilized animals and during slow-wave sleep. They consist of aperiodic, recurrent instances of large deflections (sharp waves) and synchronous fast field oscillations (ripples) in the hippocampal local-field potential [4••].

High-gamma events: Refers to periods of high-gamma oscillations in the range from 90 to 140 Hz that have been described within the rat hippocampus during sleep or immobility [51]. These periods can be identified in the local-field potential and used to define events.

EEG and MEG. The drawback of these techniques is that due to low signal-to-noise ratios (SNR) the recordings from EEG and MEG usually originate in the cortex [10,11]. Moreover, the spatial resolution of EEG/MEG is not as good as with fMRI, because the activity recorded by about 100 sensors needs to be projected onto the cortical surface. To get the best of both worlds, researchers increasingly attempt to combine the good spatial resolution of fMRI with the temporal resolution of electrophysiology recordings, for example by using combined EEG and fMRI in human subjects (reviewed in [12]). The main challenge for simultaneous EEG-fMRI recordings is the removal of gradient artefacts within the EEG recordings. This problem is particularly acute when studying spontaneous activity, because there is no experimental design that would allow gradient artefacts to only occur at non-relevant task periods [13•]. An alternative to simultaneous EEG-fMRI recordings is to record spontaneous activity from both modalities in two successive sessions. In this case, one can use MEG with its improved spatial coverage compared to EEG to record the electrophysiology. The problem in sequential recordings is the difficulty of accounting for within-subject fluctuations and potentially different brain states during the two separate recording sessions — a problem that is corroborated by the recent evidence on the importance of subsecond events and the presence of fine-grained networks.

An alternative to combined EEG/MEG fMRI recordings that solves most of their limitations is to simultaneously invasively record neural activity with fMRI. But this is only possible in animals [6] or in patient populations [14,15], where the recording sites are limited to medically indicated ones. This approach has allowed to gain valuable insights into the neurovascular coupling during spontaneous activity within the visual cortex [16••]. But in order to study the fundamental neural activity within spontaneous networks and the actual network dynamics, it will be necessary to extend this approach to multiple recording sites. For this reason, we think that the combination of fMRI with simultaneous LFP recordings as well as whole-head recordings of EEG/MEG hold great potential for future studies, as we will point out in the following sections.

Relation of spontaneous electrophysiology and BOLD recordings

First attempts to identify the neural processes underlying the RSNs in humans were conducted with simultaneous electroencephalography (EEG) and fMRI recordings [17,18]. The focus was on correlating the fMRI BOLD fluctuations to the electrophysiology recordings in the frequency range commonly studied with electrophysiology, i.e. above 2 Hz. This is achieved in several steps. First, the amplitude of the EEG signal within each band is extracted in order to study the contribution of particular oscillatory components to generating resting-state networks. Second, the amplitude modulation of the electrophysiological signal is convolved with the hemodynamic response function (HRF). The HRF is a theoretical model of the blood flow response due to neural activity and allows analysing the relationship between BOLD fluctuations and faster electrophysiological oscillations by filling out the time gap between subsequent fMRI BOLD measurements with predicted BOLD series. By regressing the individual band powers on the BOLD time series resulting from HRF convolution, the alpha power was shown to be mostly related to non-task-activated brain areas, whereas the beta-band power was mainly related to the task-activated brain areas [17]. Looking in more detail at the fMRI-based resting-state networks, D Mantini *et al.* [18] showed that each resting-state network was related to several brain rhythms. Using a different approach by not convolving the EEG signal with an HRF, T Hiltunen *et al.* [19] found that the independent components of the infraslow EEG (0.01–0.1 Hz) and BOLD fluctuations are correlated, pointing to a potentially direct relation between the BOLD and EEG signal at rest.