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The brain's resting-state activity is shaped by synchronized cross-frequency coupling of oscillatory neural activity

Esther Florin, Sylvain Baillet *

McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, 3801 University St, QC H3A 2B4, Canada

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ABSTRACT

Functional imaging of the resting brain consistently reveals broad motifs of correlated blood oxygen level dependent (BOLD) activity that engages cerebral regions from distinct functional systems. Yet, the neurophysiological processes underlying these organized, large-scale fluctuations remain to be uncovered. Using magnetoencephalography (MEG) imaging during rest in 12 healthy subjects we analyze the resting state networks and their underlying neurophysiology. We first demonstrate non-invasively that cortical occurrences of high-frequency oscillatory activity are conditioned to the phase of slower spontaneous fluctuations in neural ensembles. We further show that resting-state networks emerge from synchronized phase–amplitude coupling across the brain. Overall, these findings suggest a unified principle of local-to-global neural signaling for long-range brain communication.

1. Introduction

Over the past 15 years, there has been considerable interest in studying the resting activity of the human brain, particularly with functional magnetic resonance imaging (fMRI) (Raichle, 2011). One remarkable property of spontaneous cerebral activity is that it consistently segregates in resting-state networks (RSNs), which coincide anatomically with the major functional systems of the brain (Biswal et al., 2010). Consequently, studies suggest that RSNs provide insight into the large-scale mechanisms of healthy and impaired neural communication (Buckner et al., 2005; Tomasi and Volkow, 2012).

Yet, our current understanding of the neurophysiological mechanisms underlying these large-scale fluctuations remains elusive (Leopold and Maier, 2012; Smith, 2012). Simultaneous BOLD and electrophysiology recordings in the visual cortex of monkeys report that gamma activity of the local field potentials (LFPs) is the main electrophysiological basis of the BOLD signal (Logothetis et al., 2001; Shmuel and Leopold, 2008). These local results cannot resolve how the large-scale connectivity across the whole brain of the resting state is generated. Human magnetoencephalography (MEG) of the whole brain emphasized the contribution of alpha and beta oscillatory signals for the generation of the RSNs (Brookes et al., 2011; de Pasquale et al., 2010). This conforms well with findings that low-frequency oscillations coordinate long-range communication (von Stein et al., 2000). However, these MEG findings do not align entirely with the role of gamma oscillations in local neural activity (Buzsáki and Wang, 2012) and as counterparts of BOLD signaling (Logothetis et al., 2001).

Cross-frequency coupling, in particular phase–amplitude coupling, has been attributed an important role for communication between brain areas (Canolty and Knight, 2010; Canolty et al., 2006; Jensen and Colgin, 2007). Therefore cross-frequency coupling between a low-frequency phase and gamma activity may be an ideal candidate for the communication in the RSN. Based on these previous results we here test two hypotheses. First, interregional correlated fluctuations during rest are regulated by the coupling between the phase of slow-frequency activity and the amplitude of high-frequency oscillations. Second, this mechanism defines the principal modes of resting-state connectivity.

To test these hypotheses we use a model (megPAC), which consists of the interpolated gamma amplitude at key-events of the strongest coupling low-frequency phase. The rationale for this signal model posits that the excitability cycles of local populations need to be synchronized to form a network. Therefore, a core hypothesis is that the phases of local low-frequency oscillations emerging from communicating brain regions need to be time-locked, with no phase delay. This condition is based on evidence from the small-world architecture of brain connectivity, suggesting that cortical or subcortical hubs facilitate synchronization of distant oscillatory activity with zero-lag (i.e. with no phase delay) (Haider et al., 2006). Population excitability cycles commonly occur at lower frequencies (Osipova et al., 2008). Therefore this slower oscillatory rhythm may provide a gating mechanism that time-marks the operations of local circuits, revealed by bursts of higher-frequency activity (Buzsáki and Draguhn, 2004; Buzsáki and Wang, 2012; Lakatos et al., 2005). Along this hypothesis, an additional condition to network formation requires coherent high-frequency oscillations

* Corresponding author at: McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, 3801 University St, Montreal, QC H3A 2B4, Canada.
E-mail address: sylvain.baillet@mcgill.ca (S. Baillet).

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between regions: this would facilitate local post-synaptic integration and spiking activity to occur in concert amongst network elements. Previous observations suggest that high-frequency bursts are preferentially occurring about the trough of the low-frequency phase cycles of local field potentials (Canolty et al., 2006).

Consequently, we confirm and extend non-invasively in healthy participants for the entire brain previous observations of local phase–amplitude coupling (PAC) (Canolty et al., 2006; Osipova et al., 2008). We show that the oscillatory components conditioning the preferred timing of high-frequency activity through PAC span a relatively wide low-frequency range: from delta (2–4 Hz), theta (4–8 Hz), to alpha (8–12 Hz) bands. With these results we demonstrate that PAC contributes to the network connectivity, thereby delivering a principle for global communication across the brain at rest.

2. Materials and methods

Note that most data preprocessing and MEG source imaging were performed using Brainstorm (Tadel et al., 2011). Brainstorm is an open-source software, freely available to the academic community (http://neuroimage.usc.edu/brainstorm/). All implementation details are therefore readily documented and can be verified in Brainstorm's code.

2.1. Data acquisition

The study was approved by the local ethics committee, in accordance with the Declaration of Helsinki. 12 healthy, right-handed subjects (4 females, 8 males; age range: 21–41 y.o.) were recruited to participate in the study and all subjects gave informed consent.

The participants were tested for possible magnetic artifacts in a short preliminary MEG run. Subject preparation consisted of taping 3 to 4 head-positioning coils on the subject's scalp. The positions of the coils were measured relative to the subject's head using a 3-D digitizer system (Polhemus Isotrack). To facilitate anatomical registration with MRI, about 100 additional scalp points were also digitized. One pair of electrodes was positioned and taped across the participants' chest (one above the inferior extremity of the left rib cage and one over the right clavicle) to capture electrocardiographic (ECG) activity synchronized with the MEG traces. Similarly, one pair of electrodes was attached above and below one eye to detect eye-blinks and large saccades (EOG).

5 subjects were measured in seated position with the Elekta-Neuromag VectorView 306-channel system with a sampling rate of 2000 Hz (0.03 Hz high-pass online filter, 660 Hz anti-aliasing low-pass online filter); 7 subjects were measured in seated position using the 275-channel VSM/CTF system with a sampling rate of 2400 Hz (no high-pass filter, 660 Hz anti-aliasing online low-pass filter). Magnetic shielding was provided by magnetically-shielded rooms (MSR) with full 3-layer passive shielding for the CTF/VSM system, and single-layer shielding with Maxfilter active flux-compensation for the Elekta-Neuromag system. The combination of the two recording systems should not influence our results, because all calculations and combination of the results are performed at the source level. Moreover for task related studies it was shown that the different MEG systems yield essentially identical results (Weisend et al., 2007).

At the beginning of each MEG run, the location of the subject's head within the MEG helmet was measured by energizing the head-positioning coils, following standard procedures. For each subject, between 5 and 30 min (20 min on average for the subject group) of MEG data were acquired, during an average of 5 runs of 2 to 10-minute duration. The only instruction given to the participants was to keep their eyes open and to relax without falling asleep.

A 2-minute empty-room recording, with the same acquisition parameters, and with no subject present in the MSR, was used to capture some of the sensor and environmental noise statistics, which were used in the source estimation process, as explained below.

For subsequent cortically-constrained MEG source analysis, a T1-weighted MRI acquisition of the cerebrum was obtained from each participant either at least one month before the MEG session or afterwards.

2.2. Data pre-processing

MEG traces were pre-processed to verify data quality and to reduce contamination from artifacts (cardiac, eye movements and blinks, environmental noise). Data from the Elekta-Neuromag system were preprocessed using signal-space-separation (SSS) (Taulu et al., 2004), as implemented in the Maxfilter noise reduction system from Elekta-Neuromag. Default SSS settings were used: orders of spherical harmonic expansions for the inner and outer source models were 8 and 3, respectively. Data from the CTF/VSM system were corrected with the manufacturer's 3rd order gradient compensation system (no parameter setting required). The projectors obtained were propagated to the corresponding MEG source imaging operator.

All recordings were visually inspected to detect segments contaminated by head movements or remaining environmental noise sources, which were discarded from subsequent analysis. Heart and eye movement/blink contaminations were attenuated by designing signal-space projections (SSPs) from selected segments of data about each artifactual event (Nolte and Curio, 1999). Using Brainstorm's ECG and EOG detection functionality (Tadel et al., 2011), heartbeat events were automatically detected at the R peak of the ECG's QRS complex, and eye blink events were determined automatically at the peaks of the EOG traces. Projectors were defined using principal component analysis (PCA) of these data segments filtered between 10 and 40 Hz (for heartbeats) or 1.5 and 15 Hz (for eye blinks) in a 160-ms time window centered about the heartbeat event, or 400 ms around the eye blink event. The principal components that best captured the artifact's sensor topography were manually selected as the dimension against which the data was orthogonally projected away from, also using the routines available in Brainstorm. Note that in most subjects, the first principal component was sufficient to attenuate artifact contamination. The projectors obtained for each subject were propagated to the corresponding MEG source imaging operator as explained below. Powerline contamination (main and harmonics) was reduced by complex match filtering with 1-Hz resolution bandwidth for sinusoidal removal, also available in Brainstorm. The preprocessed data were resampled at 1000 Hz, using the polyphase filter implementation from Matlab (The Mathworks, MA, USA) with default parameters.

The scalp and cortical surfaces were extracted from the MRI volume data. A surface triangulation was obtained for each envelope using the segmentation pipeline available in Brainvisa (Rivière et al., 2009) (http://brainvisa.info), with default parameter settings and subsequently imported into Brainstorm. The individual high-resolution cortical surfaces (about 75,000 vertices per surface) were down-sampled to about 15,000 triangle vertices (also with a Brainstorm process) to serve as image supports for MEG source imaging.

2.3. MEG source imaging

Forward modeling of neural magnetic fields was performed using the overlapping-sphere technique implemented in Brainstorm (Huang et al., 1999). In this method, one sphere is automatically adjusted locally to the individual scalp surface under each magnetic sensor to compute the corresponding lead field analytically. This method has been shown to provide the best trade-off between modeling precision and numerical accuracy (Huang et al., 1999). The lead-fields were computed from elementary current dipoles distributed perpendicularly to the cortical surface from each individual (Baillet et al., 2001).

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