



Frequency-dependent functional connectivity within resting-state networks: An atlas-based MEG beamformer solution

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ARTICLE INFO

Article history:

Received 20 July 2011

Revised 27 October 2011

Accepted 2 November 2011

Available online 9 November 2011

Keywords:

Beamforming

Magnetoencephalography

Source modelling

Functional connectivity

Graph analysis

Networks

Phase lag index

Resting-state

ABSTRACT

The brain consists of functional units with more-or-less specific information processing capabilities, yet cognitive functions require the co-ordinated activity of these spatially separated units. Magnetoencephalography (MEG) has the temporal resolution to capture these frequency-dependent interactions, although, due to volume conduction and field spread, spurious estimates may be obtained when functional connectivity is estimated on the basis of the extra-cranial recordings directly. Connectivity estimates on the basis of reconstructed sources may similarly be affected by biases introduced by the source reconstruction approach. Here we propose an analysis framework to reliably determine functional connectivity that is based around two main ideas: (i) functional connectivity is computed for a set of atlas-based ROIs in anatomical space that covers almost the entire brain, aiding the interpretation of MEG functional connectivity/network studies, as well as the comparison with other modalities; (ii) volume conduction and similar bias effects are removed by using a functional connectivity estimator that is insensitive to these effects, namely the Phase Lag Index (PLI).

Our analysis approach was applied to eyes-closed resting-state MEG data for thirteen healthy participants. We first demonstrate that functional connectivity estimates based on phase coherence, even at the source-level, are biased due to the effects of volume conduction and field spread. In contrast, functional connectivity estimates based on PLI are not affected by these biases. We then looked at mean PLI, or weighted degree, over areas and subjects and found significant mean connectivity in three (alpha, beta, gamma) of the five (including theta and delta) classical frequency bands tested. These frequency-band dependent patterns of resting-state functional connectivity were distinctive; with the alpha and beta band connectivity confined to posterior and sensorimotor areas respectively, and with a generally more dispersed pattern for the gamma band. Generally, these patterns corresponded closely to patterns of relative source power, suggesting that the most active brain regions are also the ones that are most-densely connected.

Our results reveal for the first time, using an analysis framework that enables the reliable characterisation of resting-state dynamics in the human brain, how resting-state networks of functionally connected regions vary in a frequency-dependent manner across the cortex.

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Introduction

The brain consists of billions of interconnected neurons, forming an extremely complex system (Tononi and Edelman, 1998; Tononi et al., 1998) in which clusters of neurons are organised as functional units with more-or-less specific information processing capabilities (e.g. Born and Bradley, 2005; Grodzinsky, 2000). Yet, cognitive functions require the coordinated activity of these spatially separated units, where

the oscillatory nature of neuronal activity, and phase relations between units, may provide a possible mechanism (Fries, 2005; Varela et al., 2001). Not only has it been shown that rhythmic activity plays an important role in perception and sensori-motor systems (Arieli et al., 1996; Forss and Silen, 2001; Hari and Salmelin, 1997; Houweling et al., 2010; Kenet et al., 2003; Linkenkaer-Hansen et al., 2004; Mima et al., 2000), as well as in higher cognitive functions (Engel et al., 2001; Ward, 2003), but it has also been shown that patterns of resting-state oscillatory activity in patients with neurological disorders differ from those in healthy subjects, and that these differences correlate with cognitive performance (Uhlhaas and Singer, 2006).

Magnetoencephalography (MEG), with its high temporal resolution, can be used to characterise the (resting-state) networks formed

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by interacting sources of oscillatory activity (Bassett et al., 2006; Hyvarinen et al., 2010; Langheim et al., 2006; Liu et al., 2010). However, in many MEG studies the required estimation of functional connectivity is performed at the sensor-level, which impedes comparison with the rapidly growing literature on resting-state functional connectivity using functional Magnetic Resonance Imaging (fMRI; van den Heuvel and Hulshoff Pol, 2010). Another problem is that multiple recording sites pick up signals from a single source due to both the nature of the induced magnetic flux (see e.g. Domínguez et al., 2007) and volume conduction, which can lead to erroneous estimates of functional connectivity when these estimates are based on sensor-level measurements. Moreover, the signals originating from spatially separated brain areas are mixed at the sensor level, which can result in over/underestimation of synchronisation, where the exact effect is dependent on a complex interplay of modulations in source- and noise-power, source interactions, as well as relative position and orientation of the sources (e.g. Grasman et al., 2004; Meinecke et al., 2005; Schoffelen and Gross, 2009).

These limitations have provoked research into four different directions: i) using estimates of the expected functional connectivity that is due to volume conduction/field spread without true interactions, and subtracting such estimates from the measured functional connectivity (Nunez et al., 1997), or using such estimates to derive a statistical threshold for the measured interactions (e.g. Brookes et al., 2011a); ii) the development of functional connectivity estimators that are insensitive to these confounds of field spread and volume conduction (Nolte et al., 2004; Stam et al., 2007); iii) development of techniques such as DCM (Dynamic Causal Modelling; Friston et al., 2011; Moran et al., 2009) that, given a set of hypotheses, test between different bio-physically motivated source- or network-models based on their model evidence; and iv) investigations into the utility of functional connectivity analysis at the source level. The simplest approach here is to create a source model to project the (unaveraged) sensor data into source space (Hochstetter et al., 2004), although the creation of such a source montage requires the availability of averaged evoked data (see Grasman et al., 2004 though). The construction of a source montage can also be achieved by using a combination of Independent Component Analysis (ICA) and a multivariate autoregressive (MVAR) model (Gomez-Herrero et al., 2008; Haufe et al., 2010), or using Principle Component Analysis (PCA), ICA or MVAR in combination with an inverse estimator (Cheung et al., 2010; Mantini et al., 2011; Marzetti et al., 2008; Nolte et al., 2009). Alternatively, functional networks can be directly estimated at the source level (Dossevi et al., 2008), although this efficient approach is only applicable when the source matrix is obtained through a distributed linear inversion, and when the source coupling can be described as a scalar product between the source signals.

Various modifications of linear estimators have been used to reconstruct the time-series for a large number of locations (de Pasquale et al., 2010; Ghuman et al., 2011; Harle et al., 2004; Jerbi et al., 2007; Lin et al., 2004), for a set of cortical patches (e.g. David et al., 2002, 2003; Gruber et al., 2006; Palva et al., 2010a, 2010b; Supp et al., 2007), or for a limited set of a-priori defined Regions-of-Interest (ROIs; e.g. Astolfi et al., 2007; Babiloni et al., 2005; De Vico Fallani et al., 2007), where the time-series were subsequently used for the estimation of functional connectivity.

A drawback of the above approaches is that the spatially smooth estimates of neuronal activity that are obtained contain widespread correlations between reconstructed source elements, so that estimates of functional connectivity between such sources are likely to be, as with sensor-level analysis, erroneous (David et al., 2002; Hui et al., 2010) and/or difficult to interpret.

Here we propose to use a source reconstruction approach that results in sharper 3-dimensional images of neuronal activity, known as beamforming, which has recently been used to map functional connectivity across the entire brain (Brookes et al., 2011a; Guggisberg

et al., 2008; Hinkley et al., 2010; Hipp et al., 2011; Kujala et al., 2006, 2008; Martino et al., 2011; Wibral et al., 2011), or to characterise interactions between a few ROIs (Siegel et al., 2008); see also Ding et al. (2007) and Ioannides et al. (2002) for related approaches. We use beamforming to estimate time-series for a set of atlas-based ROIs that cover the brain, where the use of a standard brain-atlas aids the interpretation of our results, gives a robust platform for group-level statistics, and enables a straightforward comparison with results obtained using other modalities. Functional connectivity between these ROIs is then estimated, and we first demonstrate that the effects of volume conduction and biases introduced by the beamformer can be removed by using the Phase Lag Index (PLI) for the estimation of functional connectivity. Applying this approach to resting-state MEG data in healthy controls reveals clearly distinct frequency-band dependent patterns of resting-state functional connectivity. Generally, these patterns corresponded closely to patterns of relative source power, suggesting that the most active brain regions are also the ones that are most-densely connected.

Methods

Participants and recording protocol

We used previously analysed MEG data from 13 healthy subjects, where they formed part of studies on Parkinson's disease for which approval was obtained from the medical ethics committee of the VU University Medical Center. In these studies oscillatory power, as well as functional connectivity and network characteristics at the sensor level, were estimated and compared between healthy controls and demented and non-demented patients with Parkinson's disease (Bosboom et al., 2006, 2009).

All subjects gave written informed consent prior to participating. MEG data were acquired in the morning, using a 151-channel whole head MEG system (CTF Systems Inc., Port Coquitlam, Canada), situated in a magnetically shielded room (Vacuum-schmelze GmbH, Hanau, Germany). The data were sampled at 312.5 Hz, with a recording pass-band of 0–125 Hz, and a third-order software gradient was applied (Vrba and Robinson, 2002). Each session started with an approximately 5 minutes eyes-closed (EC) resting-state recording, followed by an approximately 5 minutes eyes-open (EO) recording. We only analysed the data recorded during the eyes-closed resting-state. Due to technical problems, 1–3 channels were discarded from the analysis (3, 3, and 7 datasets contained 148, 149, and 150 channels, respectively). For the construction of the beamformer weights, the eyes-closed data were band-pass filtered from 0.5 to 48 Hz, and after visual inspection, trials containing artefacts were removed. A time-window of, on average, 264.2 seconds (range: 175–360 s.) was used for the computation of the data covariance matrix. Broadband data were used for the estimation of the beamformer weights as this avoids overestimation of covariance between channels (Barnes and Hillebrand, 2003).

For each subject, an anatomical MRI of the head was obtained at 1 T (Impact, Siemens, Erlangen, Germany), with an in-plane resolution of 1 mm and slice thickness of 1.5 mm. Vitamin E capsules were placed at anatomical landmarks, the pre-auricular points and the nasion, to guide co-registration with the MEG data. In the MEG setting, three head position indicator coils were placed at the same fiducial locations, and these coils were activated at the start of each MEG acquisition. Head position and orientation were computed on the basis of the magnetic fields produced by these coils. Using these two corresponding sets of fiducial markers, the MEG and MRI coordinate systems were matched. The co-registered MRI was subsequently segmented, and the outline of the scalp was used to compute a multi-sphere head model (Huang et al., 1999) for the calculation of the lead-fields.

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