NeuroImage 67 (2013) 203–212

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Technical Note

Using variance information in magnetoencephalography measures of functional connectivity

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ARTICLE INFO

Article history:
Accepted 9 November 2012
Available online 17 November 2012

Keywords:
MEG
Functional connectivity
Networks
Beamformer
ICA
Hilbert envelope
Seed based correlation

ABSTRACT

The use of magnetoencephalography (MEG) to assess long range functional connectivity across large scale distributed brain networks is gaining popularity. Recent work has shown that electrodynamic networks can be assessed using both seed based correlation or independent component analysis (ICA) applied to MEG data and further that such metrics agree with fMRI studies. To date, techniques for MEG connectivity assessment have typically used a variance normalised approach, either through the use of Pearson correlation coefficients or via variance normalisation of envelope timecourses prior to ICA. Here, we show that the use of variance information (i.e. data that have not been variance normalised) in source space projected Hilbert envelope time series yields important spatial information, and is of significant functional relevance. Further, we show that employing this information in functional connectivity analyses improves the spatial delineation of network nodes using both seed based and ICA approaches. The use of variance is particularly important in MEG since the non-independence of source space voxels (brought about by the ill-posed MEG inverse problem) means that spurious signals can exist in areas of low signal variance. We therefore suggest that this approach be incorporated into future studies.

Introduction

Neuroimaging metrics of 'functional connectivity', defined as statistical interdependencies between signals from spatially separate brain regions, can be used to identify and characterise networks of communication in the human brain (e.g. Beckmann et al., 2005). Functional magnetic resonance imaging (fMRI) has been predominantly used to facilitate such measures; however fMRI is confounded since it measures a compound effect dependant on many haemodynamic parameters including blood flow, blood volume and oxygen metabolism. To avoid such confounds the use of electrophysiological recordings such as electroencephalography (EEG) or magnetoencephalography (MEG), which provide more direct measures of neural activity, are attractive as they bypass the haemodynamic response and measure electrophysiological manifestations of connectivity. Furthermore, unlike fMRI they have sufficient time resolution to measure connectivity on the millisecond time scale relevant to brain function. Recent work (Brookes et al., 2011a, 2011b; de Pasquale et al., 2010; Hipp et al., 2012; Liu et al., 2010; Luckhoo et al., 2012) has shown that a number of networks commonly observed using fMRI, including those associated with sensory action (e.g. sensorimotor network) and those associated with cognitive processing (e.g. the dorsal attention network), can also be observed in MEG data via assessment of neural oscillations.

Methods for analysis of functional connectivity in MEG data have been proposed based upon seed based correlation (Brookes et al., 2011a; Hipp et al., 2012). In these studies, MEG data are frequency filtered to a band of interest (alpha, beta etc.) and projected from sensor space to brain space using an inverse projection algorithm (e.g. Beamforming or Minimum Norm). Source space data, which are dominated by neural oscillations, are then Hilbert transformed and the amplitude envelope of the oscillatory signal calculated. A seed location is chosen based on some *a-priori* assumption, and the envelope signal from that location correlated with equivalent envelope signals for all other brain voxels in order to find areas of maximal temporal correlation. Areas showing high correlation are taken as exhibiting 'functional connectivity' with the seed location. The Pearson correlation coefficient most often employed in these techniques is derived as a normalised measure of covariance. This ensures that any variance difference between signals does not affect the metric of temporal coupling between them. However, this also means that if useful spatially specific variance information exists within the Hilbert envelope then this information is lost in the computation.

Another means to assess distributed networks in MEG is via independent component analysis (ICA). Recent work (Brookes et al., 2011b;

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1053-8119/$ – see front matter.
http://dx.doi.org/10.1016/j.neuroimage.2012.11.011

Luckhoo et al., 2012) has showed that temporal ICA, applied to Hilbert envelopes, extracts temporally independent signals whose associated spatial maps depict networks of brain regions that are spatially similar to those identified via fMRI. Further, in agreement with fMRI, similar networks are observed in resting (Brookes et al., 2011b) and task positive (Brookes et al., 2012a; Luckhoo et al., 2012) MEG data. In a number of ICA implementations (Brookes et al., 2011b, 2012a), Hilbert envelope timecourses have been normalised within each voxel; again removing variance information. In this way it is possible to ensure that 1) noise variance, which becomes artifactually large close to the centre of the head, does not dominate the variance of genuine cortical sources and 2) a single subject does not dominate group data. This normalisation makes temporal ICA similar to Pearson correlation in terms of its variance independence. However, this again means that spatially specific variance information existing within the Hilbert envelope is not employed in the network spatial characterisation.

In this technical note, we first investigate spatially specific variance information that exists in beamformer projected MEG Hilbert envelope data. We examine the spatio-spectral distribution of envelope variance, showing that, whilst at low frequencies variance is approximately evenly distributed across the cortex, at higher frequencies, functionally relevant spatial information exists. For seed based functional connectivity metrics we present a simple but useful mathematical analysis showing direct equivalence between correlation or covariance, and the linear regression parameter (effect size) for normalised or un-normalised data, respectively. In this way, we unify seed based correlation coefficients (used in previously published MEG connectivity work (Brookes et al., 2011a; Luckhoo et al., 2012)) and the more flexible linear regression framework, for which the principles of multi-subject analysis have been well established in fMRI (Woolrich et al., 2004). We then go on to show how the computation of seed based covariance (as distinct from seed based correlation) can improve spatial delineation of brain regions acting in concert. Finally, using ICA, we show evidence that the use of variance information improves the spatial delineation of distributed brain networks.

Theory and methods

Data acquisition

Data from two studies, (*resting state* and an *N-back* working memory task) are employed. Both studies have been published previously (Brookes et al., 2011a, 2012a). All MEG data were recorded using the third order synthetic gradiometer configuration of a 275 channel MEG system (MISL, Coquitlam, BC, Canada) at a sampling rate of 600 Hz. The scanner is housed inside a magnetically shielded room and a 150 Hz low pass anti-aliasing hardware filter was applied. During data acquisition the location of the subject's head within the MEG system was measured by energising 3 coils placed at fiducial points on the head (nasion, left preauricular and right preauricular). Following data acquisition, the coil positions were measured relative to the subject's head shape using a 3D digitizer (*Polhemus isotrack*). An MPRAGE structural MR image was acquired using a Philips Achieva 3 T MRI system. The locations of the fiducial markers and MEG sensors with respect to the brain anatomy were subsequently determined by matching the digitised head surface to the head surface extracted from the 3 T anatomical MRI.

Resting state study

7 healthy subjects took part in the resting state measurements. Subjects were asked to lie in the scanner with their eyes open while 300 s of resting state data were acquired. These resting state measurements were part of a longer paradigm involving a motor task (for full details see Brookes et al., 2011a); here we employ only the 300 s resting state data.

N-back study

Eight healthy subjects took part in the N-back measurements. Subjects were shown a series of letters, presented centrally in the visual field, one every 2 s with 1 s duration. Subjects were asked to press a button if the letter on the screen matched that shown N letters previously. Five conditions were employed (0, 1, 2 and 3 back and rest); for 0-back, subjects were asked to respond to an 'X'; during rest, subjects fixated on a central cross. A single epoch lasted 33 s; during the first 3 s subjects were presented with instructions on which condition was to follow; the subsequent 30 s comprised letter presentations. The number of targets per epoch was 2, 3 or 4, with each option occurring with equal probability. A single 'block' comprised 5 epochs in which all 5 conditions were presented in pseudo-random order. Each subject was presented with 12 blocks making the experiment 33 minutes in total.

Data analysis

MEG data were inspected visually and trials containing excessive interference were removed. Data were then frequency filtered into the delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and low gamma (30–50 Hz) bands using a finite impulse response filter implemented in NUTMEG (http://nutmeg.berkeley.edu, Dalal et al., 2004).

Beamforming, variance and envelope computation

Beamforming (Gross et al., 2001; Robinson and Vrba, 1998; Sekihara et al., 2006; Van Drongelen et al., 1996; Van Veen et al., 1997) estimates the electrical source strength, $\hat{Q}_{\boldsymbol{\theta}}(t)$, at a pre-determined brain space location and orientation ($\boldsymbol{\theta}$), and at time t, using a weighted sum of sensor measurements thus:

$$\hat{Q}_{\boldsymbol{\theta}}(t) = \mathbf{w}_{\boldsymbol{\theta}}^{\mathrm{T}}\mathbf{m}(t) \tag{1}$$

where $\mathbf{m}(t)$ is a vector of magnetic field measurements made at M sensors at time t and $\mathbf{w}_{\boldsymbol{\theta}}$ is a vector of weighting parameters tuned to location and orientation $\boldsymbol{\theta}$. Superscript T indicates a transpose. Weights ($\mathbf{w}_{\boldsymbol{\theta}}$) are derived based on minimising the variance of the output timecourse (i.e. $\varepsilon\left(\hat{Q}_{\boldsymbol{\theta}}^2\right)$) but with a linear constraint that variance originating at $\boldsymbol{\theta}$ remains (here ε denotes expectation value). Mathematically the weights are given by:

$$\mathbf{w}_{\boldsymbol{\theta}}^{\mathrm{T}} = \left[\mathbf{h}_{\boldsymbol{\theta}}^{\mathrm{T}}\{\mathbf{C}+\mu\boldsymbol{\Sigma}\}^{-1}\mathbf{h}_{\boldsymbol{\theta}}\right]^{-1}\mathbf{h}_{\boldsymbol{\theta}}^{\mathrm{T}}\{\mathbf{C}+\mu\boldsymbol{\Sigma}\}^{-1} \tag{2}$$

where $\mathbf{h}_{\boldsymbol{\theta}}$ is the lead field vector for location and orientation $\boldsymbol{\theta}$, $\mathbf{C}$ represents the data covariance matrix and $\boldsymbol{\Sigma} = \eta^2\mathbf{I}$ where η^2 represents an estimate of the white noise at each MEG sensor (estimated as the smallest singular value of $\mathbf{C}$). $\mathbf{I}$ is the identity matrix and μ (here given a value of 4) is a regularisation parameter. For both resting state and N-back data, beamformer projected timecourses were estimated for a set of locations placed at the vertices of a regular 8 mm grid spanning the entire brain. Lead fields were based on a dipole current model (Sarvas, 1987) and a local-sphere head model (Huang et al., 1999). Source orientation at each voxel was computed using a non-linear search for the maximum projected signal to noise ratio, Z_{opt},

$$Z_{\mathrm{opt}} = \max_{\delta}\left(\frac{\mathbf{w}_{\boldsymbol{\theta}}^{T}\mathbf{C}\mathbf{w}_{\boldsymbol{\theta}}}{\mathbf{w}_{\boldsymbol{\theta}}^{T}\boldsymbol{\Sigma}\mathbf{w}_{\boldsymbol{\theta}}}\right), 0^{\circ} \le \delta \le 180^{\circ}. \tag{3}$$

Where δ takes a value between 0 and 180° and denotes the source orientation which was restricted to the tangential plane (computed relative to the mean of the local spheres). The result for a single subject is a timecourse of electrical activity spanning the whole experiment, sampled at 600 Hz, for every voxel in source space.