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Optimising experimental design for MEG resting state functional connectivity measurement

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ABSTRACT

The study of functional connectivity using magnetoencephalography (MEG) is an expanding area of neuroimaging, and adds an extra dimension to the more common assessments made using fMRI. The importance of such metrics is growing, with recent demonstrations of their utility in clinical research, however previous reports suggest that whilst group level resting state connectivity is robust, single session recordings lack repeatability. Such robustness is critical if MEG measures in individual subjects are to prove clinically valuable. In the present paper, we test how practical aspects of experimental design affect the intra-subject repeatability of MEG findings; specifically we assess the effect of co-registration method and data recording duration. We show that the use of a foam head-cast, which is known to improve co-registration accuracy, increased significantly the between session repeatability of both beamformer reconstruction and connectivity estimation. We also show that recording duration is a critical parameter, with large improvements in repeatability apparent when using ten minute, compared to five minute recordings. Further analyses suggest that the origin of this latter effect is not underpinned by technical aspects of source reconstruction, but rather by a genuine effect of brain state; short recordings are simply inefficient at capturing the canonical MEG network in a single subject. Our results provide important insights on experimental design and will prove valuable for future MEG connectivity studies.

Introduction

The measurement of covariation between neuroimaging signals generated in spatially separate brain regions facilitates the elucidation and characterisation of brain networks (Beckmann et al., 2005; Corbetta et al., 1998; Fox et al., 2005; Fox and Raichle, 2007; Friston, 1994; Raichle et al., 2001; Smith et al., 2009). These networks, and the functional connectivities that define them, are thought to support core mental processes with some related to sensory processing and others associated with high level cognition. Because these networks can be observed even when subjects are notionally "at rest" (i.e. no specific task paradigm is used) they are often termed resting state networks (RSNs) (Beckmann et al., 2005). Although predominantly measured using functional magnetic resonance imaging (fMRI), a growing body of work shows that network characterisation via magnetoencephalography (MEG) offers novel insights into the neural mechanisms that underlie functional connectivity (Hall et al., 2014; O'Neill et al., 2015a; Schölvinck et al., 2013). MEG involves assessment of the magnetic fields that are induced outside the head by neural current flow in the brain. Mathematical modelling of these fields subsequently allows construction of 3D images showing moment to moment changes in brain current. Because MEG signals are generated directly by neurons, the electrophysiological basis of connectivity can be probed. Furthermore, the excellent temporal precision afforded by MEG allows estimation of dynamic changes in network structure (Baker et al., 2014; Brookes et al., 2014; O'Neill et al., 2015a). The importance of characterising electrophysiological connectivity is growing, with numerous demonstrations that connections are perturbed in pathologies (Brookes et al., 2016; Friston, 1998; Guggisberg et al., 2008; Kessler et al., 2014; Palaniyappan and Liddle, 2012; Schnitzler and Gross, 2005; Stufflebeam et al., 2011; Tewarie et al., 2014; van Dellen et al., 2012). However, demonstrations have typically been made on large subject groups, with little attention paid to the accuracy of measurements within individual subjects. Such accuracy is critical if MEG connectivity is to provide diagnostic and clinically relevant information.

To date, most studies that have examined the robustness of MEG connectivity estimation suggest relatively poor reproducibility. For

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example, Wens et al. (2014) showed that whilst group level connectivity within several well-known networks is stable, there is significant variability at the individual subject level. Colclough et al. (2016) tested the between session repeatability of a large number of functional connectivity measurements, showing that although group level inference is reliable, network metrics vary across individuals. The authors also showed that even separate measures in a single subject lack reproducibility. Tewarie et al. (2016) used MEG to predict the canonical RSNs observed in fMRI; whilst predictions were robust at the group level, they fared less well within individuals and no significant inter-individual differences in connectivity were predicted. Similarly, O'Neill et al. (2016) showed that dynamic measures of functional connectivity are also variable across subjects. Although the reason for this poor reliability is not well understood, it likely results from a combination of genuine differences (Finn et al., 2015) (i.e. even within a single subject, differences in brain state between two experimental recordings could generate marked differences in network connectivity) and instrumental imprecision. Regarding the latter, MEG has relatively low signal-to-noise ratio (SNR) since environmental and biomagnetic fields of no interest (e.g. from lab equipment, heart and muscles) are larger than neuromagnetic fields. In addition, source localisation (reconstructing images of current density using extracranial magnetic fields) is based upon an ill-posed problem which reduces spatial resolution. Another significant limitation is co-registration error. The accuracy of source localisation is dependent not only on data quality, but also on precise forward models (models of magnetic fields that would be observed at the sensors given a known current distribution). Forward models, in turn, require accurate knowledge of the location and orientation of MEG sensors relative to brain anatomy. Importantly (and perhaps counterintuitively) as SNR is increased, the requirement for high spatial precision also increases. Unfortunately at present, co-registration usually relies on digitisation and surface matching procedures which can cause errors of several millimetres that propagate into source reconstructions. If the potential of MEG to characterise network connectivity in individual subjects is to be realised, then these sources of error must be minimised.

Here, using simulations and experiments, we probe how test-retest repeatability of functional connectivity in MEG can be optimised by changing practical aspects of experimental design. We concentrate on two parameters: recording duration and co-registration method. It is clear that longer recordings will maximise SNR, and previous work (Brookes et al., 2010; Brookes et al., 2008) shows that source reconstruction accuracy and spatial resolution are improved as recording duration (or bandwidth) is increased. Here, using simulated and experimental MEG data, we investigate the effect that changing recording duration has on network connectivity. Investigating the effect of co-registration error in real MEG data is challenging since such errors are inherent to all experimental measures and no ground truth is known. Here, we address this issue by adopting a recently developed approach, employing foam head-casts (constructed using 3D printing) (Troebinger et al., 2014). The internal surface of these head-casts fits to the subject's scalp, whilst the external surface fits the MEG scanner helmet. In this way we are able to lock the head in place, minimising motion and co-registration error. In what follows, we will show that recording duration and co-registration have a marked effect on the repeatability of source localisation, and functional connectivity. Our results will provide advice for the design of future scanning protocols, particularly in studies of individual subjects.

Simulations

In order to examine the effect of co-registration error and recording duration on connectivity estimation, we first undertook a set of simulations. All simulations were based upon the geometry of a CTF 275-channel axial gradiometer system (5 cm baseline) operating in third-order gradiometer configuration. Brain anatomy, head shape, and system geometry were based upon a real experimental recording session. In everything that follows, the simulated sampling frequency was 600 Hz; all simulated sources were assumed to be dipolar; the forward field was computed using a multiple local sphere head model and the formula derived by Sarvas (1987). The locations of all simulated sources were set according to the centre of mass of 78 anatomically defined cortical regions, extracted from the automated anatomical labelling (AAL) atlas.

Simulation methods

Simulated data

Two dipoles, henceforth known as the seed and test dipole, were simulated in homologous regions of somatosensory cortex, with locations and orientations represented by $\boldsymbol{\theta}_{seed}$ and $\boldsymbol{\theta}_{test}$ respectively (i.e. $\boldsymbol{\theta}$ represents both location (set according to the AAL regions) and orientation, which was confined to the tangential plane and set at a random angle with respect to the azimuthal direction). The dipole time courses, denoted $q_{seed}(t)$ and $q_{test}(t)$, were simulated in order to mimic genuine functional connectivity between regions. Mathematically,

$$q_{seed}(t) = b(t) + e_1(t), \tag{1}$$

and

$$q_{test}(t) = b(t + \tau) + e_2(t). \tag{2}$$

Here, $b(t)$ was generated by frequency filtering Gaussian noise into the beta band (13–30 Hz). This was added to $q_{seed}(t)$ and a time/phase shifted version was added to $q_{test}(t)$ in order to simulate functional connectivity between locations. In addition, $e_1(t)$ and $e_2(t)$, which represent two orthogonal beta band filtered Gaussian noise time courses, with amplitude equal to 30% of $b(t)$, were added. In this way, the simulated time courses represent regional brain signals which exhibit partial connectivity. Note that $\tau = 10\,ms$. To make the simulation more realistic, in addition to the seed and test dipoles, we simulated a further 76 dipoles located at the centres of mass of the remaining AAL regions. These "dipoles of no interest" had amplitude equal to 5% of the seed and test signals. The final dataset was simulated as

$$\boldsymbol{B}(t) = a_{seed}\boldsymbol{l}(\boldsymbol{\theta}_{seed})q_{seed}(t) + a_{test}\boldsymbol{l}(\boldsymbol{\theta}_{test})q_{test}(t) + \left(\sum_{i=1}^{76} a_i\boldsymbol{l}(\boldsymbol{\theta}_i)q_i(t)\right) + \boldsymbol{E}(t). \tag{3}$$

Here, a_{seed} and a_{test} represent the amplitudes of the seed and test dipoles respectively. $\boldsymbol{l}(\boldsymbol{\theta})$ represents the forward field for location/orientation $\boldsymbol{\theta}$. The summation represents the contribution of the dipoles of no interest and $\boldsymbol{E}(t)$ represents sensor level interference. Notice that $\boldsymbol{B}(t)$, $\boldsymbol{E}(t)$ and $\boldsymbol{l}(\boldsymbol{\theta})$ are vectors of dimension $N_{chans}\times 1$, where N_{chans} represents the number of MEG sensors. $\boldsymbol{E}(t)$ was generated using real MEG data from an empty room noise recording, acquired using a 275-channel CTF system in third-order gradiometer configuration, and filtered into the beta band. The simulated SNR (defined as the ratio of the norms of the field from all dipoles and the interference field) was set to 1.

Beamformer reconstruction

Following simulation of MEG data, reconstruction in source space was achieved via beamforming. Briefly, an estimate of electrical source strength, $\hat{q}(\boldsymbol{\theta},t)$, at cortical location and orientation $\boldsymbol{\theta}$ was given by a weighted sum of sensor measurements so that:

$$\hat{q}(\boldsymbol{\theta}, t) = \boldsymbol{w}^T(\boldsymbol{\theta})\mathbf{B}(\mathrm{t}) \tag{4}$$

Note that the 'hat' notation represents an estimate; i.e. $\hat{q}$ is the