NeuroImage 91 (2014) 282–299

Contents lists available at ScienceDirect

NeuroImage

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

Measuring temporal, spectral and spatial changes in electrophysiological brain network connectivity

Matthew J. Brookes [a,*], George C. O'Neill [a], Emma L. Hall [a], Mark W. Woolrich [b,c], Adam Baker [b], Sofia Palazzo Corner [a], Siân E. Robson [a], Peter G. Morris [a], Gareth R. Barnes [d]

[a] Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, University Park, Nottingham, UK
[b] Oxford Centre for Human Brain Activity, University of Oxford, Warneford Hospital, Oxford, UK
[c] Oxford Centre for Functional MRI of the Brain, University of Oxford, John Radcliffe Hospital, Oxford, UK
[d] Wellcome Trust Centre for Neuroimaging, University College London, London, UK

ARTICLE INFO

Article history:
Accepted 31 December 2013
Available online 10 January 2014

Keywords:
MEG
Functional connectivity
Neural oscillations
Non-stationarity
Brain networks
Canonical correlation
Multi-variate
Leakage reduction

ABSTRACT

The topic of functional connectivity in neuroimaging is expanding rapidly and many studies now focus on coupling between spatially separate brain regions. These studies show that a relatively small number of large scale networks exist within the brain, and that healthy function of these networks is disrupted in many clinical populations. To date, the vast majority of studies probing connectivity employ techniques that compute time averaged correlation over several minutes, and between specific pre-defined brain locations. However, increasing evidence suggests that functional connectivity is non-stationary in time. Further, electrophysiological measurements show that connectivity is dependent on the frequency band of neural oscillations. It is also conceivable that networks exhibit a degree of spatial inhomogeneity, i.e. the large scale networks that we observe may result from the time average of multiple transiently synchronised sub-networks, each with their own spatial signature. This means that the next generation of neuroimaging tools to compute functional connectivity must account for spatial inhomogeneity, spectral non-uniformity and temporal non-stationarity. Here, we present a means to achieve this via application of windowed canonical correlation analysis (CCA) to source space projected MEG data. We describe the generation of time–frequency connectivity plots, showing the temporal and spectral distribution of coupling between brain regions. Moreover, CCA over voxels provides a means to assess spatial non-uniformity within short time–frequency windows. The feasibility of this technique is demonstrated in simulation and in a resting state MEG experiment where we elucidate multiple distinct spatio-temporal-spectral modes of covariation between the left and right sensorimotor areas.

Introduction

Traditional analysis of neuroimaging data has focussed on the identification of significant changes in some metric of interest that are time locked to a particular task. Such methodologies usually rely on knowledge of task timing, and in some cases accurate models of the temporal evolution of neuroimaging signals which are then compared to measured data. These techniques have proved effective in highlighting brain regions that are involved in sensory and cognitive tasks. However, the last decade has seen a 'paradigm shift' in functional brain imaging (Raichle, 2009), with traditional analyses increasingly complemented by analysis of functional connectivity (Beckmann et al., 2005; Biswal et al., 1995; Deco and Corbetta, 2011; Fox and Raichle, 2007; Fox et al., 2005). Here, researchers seek to elucidate spatial patterns of temporal covariation between brain regions. Significant statistical interdependency (e.g. assessed via temporal correlation (Biswal et al., 1995) or independent component analysis (Beckmann et al., 2005)) between signals originating in two or more spatially separate anatomical regions is usually taken to mean that those regions are 'connected'. Functional magnetic resonance imaging (fMRI) has become the most popular technique for mapping these networks of connectivity and this has led to the exciting discovery of a relatively small number of large scale distributed brain networks (Beckmann et al., 2005). These networks appear to be heterogeneous in function (Deco and Corbetta, 2011), with some associated with sensory control (e.g. the sensorimotor network) and others relating to cognition and attention (e.g. the dorsal attention network). Networks have been shown to be highly reproducible across subjects, and observable both in the presence and absence of a task (Smith et al., 2009).

In many studies, the methods used to probe connectivity between regions assess temporal correlation over the duration of the measurement, typically several minutes. This approach necessarily assumes

* Corresponding author at: Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, University Park, Nottingham NG7 2RD, UK.
E-mail address: matthew.brookes@nottingham.ac.uk (M.J. Brookes).

http://dx.doi.org/10.1016/j.neuroimage.2013.12.066
1053-8119/

that functional connectivity is stationary in time, over the duration of the experiment, and can be captured entirely by a single value of time averaged correlation. However, over a decade of theoretical (e.g. Friston, 1997, 2000), computational (e.g. Breakspear et al., 2003; Deco et al., 2009; Ghosh et al., 2008; Honey et al., 2007) and empirical (e.g. Bassett et al., 2006; Breakspear et al., 2004) evidence suggests that complex and highly temporally variable neuronal dynamics underlie the coupling observed between spatially separate brain regions. Recent studies have explored the temporal evolution of correlation between regions using neuroimaging data. For example, Chang and Glover (2010) employed fMRI to show that functional connectivity is highly variable over time. Further, using magnetoencephalography (MEG), De Pasquale and colleagues have published multiple papers (de Pasquale et al., 2010, 2012) showing that accounting for temporal non-stationarity aids in the detection of several resting state networks, suggesting that networks transiently engage with other networks during periods of high internal correlation, with the default mode network acting as a hub of cross network interaction. Also using MEG, Baker et al. (2012) show evidence of a bi-state nature to band limited power correlation, with periods of zero functional connectivity interspersed with periods of high transient functional connectivity. These findings imply that assessing temporal variability in functional connectivity may provide valuable insight into the neurophysiology of functional networks.

In addition to non-stationarity in time, functional connectivity (as measured by electrophysiological techniques) has also been shown to vary across frequency bands. For example, band limited amplitude envelope correlation between the left and the right motor cortices is maximised in the alpha and beta bands, with correlation failing to reach significance at low frequency (i.e. 1–8 Hz) or high frequency (i.e. >40 Hz) (Brookes et al., 2012b). Indeed this finding has been mirrored by other MEG studies (Hipp et al., 2012), and is in general agreement with findings from simultaneous electroencephalography (EEG)/fMRI. The origins of the instability of functional connectivity across frequency bands is shown, to a degree, in a recent paper (Brookes et al., 2012a) which measured the time–frequency evolution of neural oscillatory amplitude in four nodes of a fronto-parietal network during a cognitive task. Results highlighted that in all four nodes, beta power exhibited a monotonic reduction with increased task difficulty. However, stimulus related increases in theta power within this network were only observable in the frontal regions whilst stimulus related decreases in alpha power were only observable in the parietal nodes. In other words, network connectivity, as determined by electrophysiological techniques, is not only non-stationary in time, but also specific to relatively narrow frequency ranges.

Most studies assess functional connectivity either between two spatially separate point locations (i.e. between two voxels), or between two voxel clusters, with signals averaged across voxels within those clusters. This means that, in the same way that time averaged functional connectivity metrics cannot account for temporal non-stationarity, they also cannot account for spatial inhomogeneity. Taking, for example, the sensori-motor network, it is well known that separate sub-regions within the sensorimotor network are mapped somatotopically (i.e. mapped to separate areas of the body (Sanchez-Panchuelo et al., 2012)). Functional connections may be investigated between any pair of sub-regions within the sensori-motor network, and it is entirely conceivable that temporal non-stationarity between individual voxels, or small clusters, may be (in part) due to spatial inhomogeneity within the network. For example, the two somatotopic regions mapped to the left and right index fingers may exhibit a functional connection in time window A, and likewise the two regions related to the left and right ring fingers may exhibit a functional connection in time window B. Assessment of connectivity between single voxels may therefore only characterise one temporal aspect of connectivity whilst averaging across voxels in large clusters will necessarily spatially blur these effects, as well as introducing increased noise by averaging voxels that do not exhibit correlation.

The above arguments suggest that the next generation of neuroimaging tools to investigate functional connectivity will require the ability to assess temporal non-stationarity, as well as spectral structure and spatial inhomogeneities within (and across) the observed networks. With this in mind, it is noteworthy that electrophysiological metrics such as MEG have significant advantages over fMRI: increased time resolution offers advantages in characterising temporal non-stationarity whilst the direct nature of MEG allows a non-invasive window on neural oscillations, and therefore spectral structure. In this paper, we introduce a novel technique to characterise functional connectivity, based upon beamforming (Brookes et al., 2008; Gross et al., 2001; Robinson and Vrba, 1998; Sekihara et al., 2006; Van Veen et al., 1997) and canonical correlation analysis (CCA) (Barnes et al., 2011; Brookes et al., 2012b; Soto et al., 2010). We extend work presented in our previous papers (Brookes et al., 2011a, 2012b; Hall et al., 2013) by developing a method capable of measuring the temporal, spectral and spatial variation in functional connectivity, assessed by band limited envelope correlation. Specifically, we use a sliding window to map temporal non stationarity; temporal filtering to detect frequency specific functional connectivity and, most importantly, we apply the multivariate CCA approach across voxels, to characterise the spatial representation of functional connectivity without the need for single seed voxel assessment or cluster averaging. In what follows, the Theory section presents the theoretical basis of CCA within a beamformer framework. In the Simulations section we show how CCA can achieve the aims set out above. The Real MEG data section shows application of CCA to real MEG data, examining resting state sensorimotor network connectivity. Finally results are discussed and conclusions drawn in the last section.

Theory

Electrophysiological signals are rich in information and the term 'functional connectivity', loosely defined as a statistical dependency between signals originating from different brain regions, can mean a number of things (see e.g. Schölvinck et al., 2013). Throughout the remainder of this manuscript, we use the term functional connectivity to mean temporal correlation between the amplitude envelopes of band limited neural oscillations (Brookes et al., 2011a,b; de Pasquale et al., 2010; Hall et al., 2013; Hipp et al., 2012; Liu et al., 2010; Luckhoo et al., 2012).

Source localisation and selection of voxel clusters

Characterisation of functional connectivity between two voxel clusters using MEG data necessarily requires that electrophysiological signals are assessed in source space (i.e. extra-cranial magnetic field data are projected into the brain). There are several advantages of source space projection in connectivity assessment (Schoffelen and Gross, 2009). Firstly, results can be overlaid directly onto structural brain images, enabling direct interpretation with respect to underlying anatomy. Secondly, source localisation (via adaptive techniques such as beamforming) Reduces artifacts in MEG data (Sekihara et al., 2001, 2006), meaning that the signal to noise ratio (SNR) of projected data is higher than the SNR of raw data in channel space. This second point is often overlooked, but of critical importance in this context since artefacts caused by common interference across MEG channels (from e.g. the heart) may generate spurious connectivity measurements (Brookes et al., 2011a).

Here, source space projection is achieved via beamforming (Brookes et al., 2008; Gross et al., 2001; Robinson and Vrba, 1998; Sekihara et al., 2001; Van Drongelen et al., 1996; Van Veen et al., 1997); a popular methodology that has been well characterised in previous papers. Briefly, using a beamformer, an estimate of electrical source strength is made at some predetermined location in the brain, using a weighted sum of MEG sensor measurements. The weighting parameters are derived based on power minimisation; the overall power in the output signal is