NeuroImage 67 (2013) 331–343

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

Evaluation and calibration of functional network modeling methods based on known anatomical connections

Debra Ann Dawson [a,b,e], Kuwook Cha [a,b,c], Lindsay B. Lewis [a,c,e], Janine D. Mendola [c,e], Amir Shmuel [a,b,d,e,*]

[a] Montreal Neurological Institute, Montreal, QC, Canada
[b] Department of Neurol. and Neurosurg., Montreal, QC, Canada
[c] McGill Vision Res., Montreal, QC, Canada
[d] Department of Biomedical Eng., Montreal, QC, Canada
[e] McGill University, Montreal, QC, Canada

ARTICLE INFO

Article history:
Accepted 5 November 2012
Available online 12 November 2012

Keywords:
Resting-state
Resting-state networks
Spontaneous activity
Functional connectivity
Correlation
Partial correlation
Coherence
Generalized synchronization
Granger causality
Patel's conditional dependence
Bayesian network

ABSTRACT

Recent studies have identified large scale brain networks based on the spatio-temporal structure of spontaneous fluctuations in resting-state fMRI data. It is expected that functional connectivity based on resting-state data is reflective of — but not identical to — the underlying anatomical connectivity. However, which functional connectivity analysis methods reliably predict the network structure remains unclear. Here we tested and compared network connectivity analysis methods by applying them to fMRI resting-state time-series obtained from the human visual cortex. The methods evaluated here are those previously tested against simulated data in Smith et al. (Neuroimage, 2011).

To this end, we defined regions within retinotopic visual areas V1, V2, and V3 according to their eccentricity in the visual field, delineating central, intermediate, and peripheral eccentricity regions of interest (ROIs). These ROIs served as nodes in the models we study. We based our evaluation on the "ground-truth", thoroughly studied retinotopically-organized anatomical connectivity in the monkey visual cortex. For each evaluated method, we computed the fractional rate of detecting connections known to exist ("c-sensitivity"), while using a threshold of the 95th percentile of the distribution of interaction magnitudes of those connections not expected to exist.

Under optimal conditions — including session duration of 68 min, a relatively small network consisting of 9 nodes and artifact-free regression of the global effect — each of the top methods predicted the expected connections with 67–85% c-sensitivity. Correlation methods, including Correlation (Corr; 85%), Regularized Inverse Covariance (ICOV; 84%) and Partial Correlation (PCorr; 81%) performed best, followed by Patel's Kappa (80%), Bayesian Network method PC (BayesNet; 77%), General Synchronization measures (67–77%), and Coherence (CohB; 74%). With decreased session duration, these top methods saw decreases in c-sensitivities, achieving 59–76% for 17 min sessions. With a short resting-state fMRI scan of 8.5 min, none of the methods predicted the real network well, with Corr (65%) performing best. With increased complexity of the network from 9 to 36 nodes, multivariate methods including PCorr and BayesNet saw a decrease in performance. Artifact-free regression of the global effect increased the c-sensitivity of the top-performing methods. In an overall evaluation across all tests we performed, correlation methods (Corr, ICOV, and PCorr), Patel's Kappa, and BayesNet method PC set themselves somewhat above all other methods.

We propose that data-based calibration based on known anatomical connections be integrated into future network studies, in order to maximize sensitivity and reduce false positives.

Introduction

One of the most widely used and insightful methods for measuring activity in the brain is functional Magnetic Resonance Imaging (fMRI; Kwong et al., 1992; Ogawa et al., 1992; Bandettini et al., 1992). Efforts are constantly being made to improve processing techniques, data interpretation, and modeling of such data. A widely used analysis method is that of computing functional connectivity measures associated with resting-state data, obtained in the absence of a task (Biswal et al., 1995). The term "functional connectivity" refers to the correlations between spatially remote neurophysiological events. While this is the working definition, measures other than correlation per se can quantify a relationship in the temporal domain between neurophysiological events. Here we evaluate the performance of network modeling methods applied to resting-state fMRI time-series obtained from the human brain.

* Corresponding author at: Montreal Neurological Institute, Montreal, QC, Canada. Fax: +1 514 398-8106.
E-mail address: amir.shmuel@mcgill.ca (A. Shmuel).

1053-8119/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2012.11.006

Past considerations to modeling of networks using fMRI data have found that careful model design and selection are required for the results of the study to achieve a semblance of validity. The more robust the model is, the more accuracy we can expect from the model. Specifically, successful models include as many network confounds as possible, such as forward, backward, or cyclic connections (Friston, 2011) as well as any number of foreseeable contributions from non-neuronal, physiological sources (Fox and Raichle, 2007). Flexibility is also an important quality in a model; it should be able to represent the parameters and conditions of a wide array of experiments (Roebroeck et al., 2009).

A major shortcoming of many network models is the inability to distinguish indirect from direct connections based on fMRI data (Fox and Raichle, 2007). Such a task is even more difficult when analyzing strong activations such as in fMRI experiments with stimulus presentation. Studying functional connectivity with measurements of task evoked responses has been useful in identifying larger brain regions which co-activate (Bullmore et al., 1996; Calhoun et al., 2001; Mizuhara et al., 2004); however due to the strength of the responses and the fact that they are time-locked to the onset of a stimulus or a task, the details achievable in these connectivity analyses are limited. It has been suggested that the much lower amplitude signal of resting-state activity is a fraction of the task response amplitude (Jiang et al., 2004; Ng et al., 2011) and thus that connectivity analyses of the brain at rest may give insight into functional connectivity at a finer scale. However, although spontaneous fluctuations in fMRI signals correlate with the locally measured neurophysiological activity (Shmuel and Leopold, 2008; Schoelvinck et al., 2010), functional connectivity between fMRI signals recorded in two remote regions may reflect network effects rather than a direct connection between these regions. Therefore, it is expected that functional connectivity based on resting-state data is reflective of anatomical connections (De Luca et al., 2006; Fox and Raichle, 2007; Koch et al., 2002; Quigley et al., 2003; van den Heuvel et al., 2009), although this reflection is not trivially identical (Honey et al., 2010).

In a recent paper by Smith et al. (2011), the abilities of various network models to correctly predict networks of simulated fMRI data were evaluated. The simulations considered a range of scenarios, including variations in number of nodes, session durations, connection strengths, input strengths, and other potential confounds thought to be present in real fMRI data. The main result was that, with simulated data, Partial Correlation, Inverse Covariance, and Bayesian network models could often predict over 90% of correct network edges with greater connection strengths than the 95th percentile of the false positive distribution. This being said, even these strongest methods showed weakness when faced with some of the tested confounds, indicating a necessity to test the model performances with real data, where any number of confounds may be significant.

Here we explore the validity of various network modeling methods by evaluating their successes at predicting expected anatomical connections between different regions in the human visual cortex. We chose retinotopic visual areas V1, V2, and V3 for pursuing this evaluation because of the in depth understanding we have of the anatomical connections within and between these areas based on studies of the macaque monkey brain. The methods we test here against human resting-state data are those previously tested against simulated data in a paper by Smith et al. (2011). Our goal is to identify the most appropriate models for use with real human resting-state fMRI data. To quantify a method's ability to accurately predict a set of connections, we use measures of “c-sensitivity”, a term coined by Smith et al. representing the fractional rate of detecting true connections. We found that Partial Correlation, Regularized Inverse Covariance and Bayesian Network methods achieved the highest c-sensitivities across tests. We propose to improve data-acquisition parameters and analysis by integrating a data-driven calibration into functional connectivity studies.

Methods

Data acquisition and preprocessing

Subjects and scanning sessions

Seven normally sighted subjects participated in this study after giving written consent in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). For the analysis presented here, we excluded the data obtained from2 of the subjects (see below). Each subject was scanned in two sessions: one to obtain high-resolution anatomical images and fMRI for retinotopy and the other to obtain high-resolution anatomical images and fMRI in the resting-state. During the retinotopic mapping scans, the subjects were instructed to fixate their eyes on a fixation spot at the center of the screen through a projection mirror. During the resting-state functional scans, the subjects kept their eyes closed.

MRI data acquisition

Data were acquired on a 3 T Magnetom TIM Trio scanner (Siemens, Erlangen, Germany). A phased array head coil was used, with 20 and 32 channels employed for retinotopy mapping and resting-state scans, respectively. Echo-planar imaging was used to measure blood oxygenation level-dependent (BOLD) changes in image intensity. Resting-state functional MRI was pursued in 8 runs per each subject. Each run consisted of 256 contiguous EPI whole-brain functional volumes [repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle = 90°; 30 slices; matrix = 112 × 112; field of view (FOV) = 224 mm; acquisition voxel size = 2 × 2 × 2.2 mm]. Retinotopic mapping was pursued with axial-oblique slices [repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle = 90°; 28 slices; matrix = 128 × 128; field of view (FOV) = 263 mm; acquisition voxel size = 2.05 × 2.05 × 3 mm]. In both sessions, T1-weighted (MPRAGE) anatomical volumes were acquired with high resolution (1 × 1 × 1 mm) for between session co-registration of the fMRI data.

Retinotopic mapping and definition of visual areas

The visual cortex's functional organization corresponds spatially to the inverse of the visual field representation, a phenomenon called retinotopy (Inouye, 1900; Holmes, 1945). Using retinotopic analysis we can identify a hierarchy of regions which process different sub-fields of the visual field and at different levels of detail. Here we focus on visual areas V1, V2, and V3, further defining the ROIs according to their eccentricities in the visual field. Visual areas V1, V2, and V3 of each subject were defined according to conventional phase encoding retinotopy (Engel et al., 1994; Larsson and Heeger, 2006; Sereno et al., 1995). The visual stimuli were projected from a liquid crystal display (LCD) projector at 1024 × 768 resolution and 60 Hz refresh rate onto a translucent screen at the end of the scanner bore. The subjects viewed the screen at the total viewing distance of 138 cm through a mirror mounted to the coil, which yielded 33×25° (41° along the diagonal) of viewing angle. During the retinotopic mapping scans, the conventional retinotopy mapping stimulus of expanding/contracting rings or clockwise/counter-clockwise rotating wedges periodically traversed the visual field every 64 seconds. The width and expansion/contraction speed of the ring stimulus were logarithmically changed as a function of eccentricity in consideration of the cortical magnification factor whereas the arc angle of wedge stimulus was constant at 10°. The ring and the wedge stimuli consisted of checkerboard patterns where brightness and colors changed at a rate of 8 Hz to maximize the neural responses of the visual areas of interest. In order to aid the subjects in maintaining their fixation, it was requested that they report any change in the direction of a 0.5° arrowhead which randomly changed directions (up, down, left, right) using a fibre-optic button box.

In order to define visual areas, the temporal phases of the travelling waves of fMRI responses evoked by the ring and wedge stimuli were matched to the visual field locations in the polar coordinate system: