NeuroImage 90 (2014) 196–206

Contents lists available at ScienceDirect

NeuroImage

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

Dynamic changes of spatial functional network connectivity in healthy individuals and schizophrenia patients using independent vector analysis

Sai Ma [a,*], Vince D. Calhoun [b,c], Ronald Phlypo [a], Tülay Adalı [a]

[a] Dept. of CSEE, University of Maryland, Baltimore County, Baltimore, MD 21250, USA
[b] The Mind Research Network, Albuquerque, NM 87106, USA
[c] Dept. of ECE, University of New Mexico, Albuquerque, NM 87131, USA

ARTICLE INFO

Article history:
Accepted 30 December 2013
Available online 10 January 2014

Keywords:
Dynamic spatial change
Spatial functional network connectivity
Independent vector analysis
fMRI
Schizophrenia

ABSTRACT

Recent work on both task-induced and resting-state functional magnetic resonance imaging (fMRI) data suggests that functional connectivity may fluctuate, rather than being stationary during an entire scan. Most dynamic studies are based on second-order statistics between fMRI time series or time courses derived from blind source separation, e.g., independent component analysis (ICA), to investigate changes of temporal interactions among brain regions. However, fluctuations related to spatial components over time are of interest as well. In this paper, we examine higher-order statistical dependence between pairs of spatial components, which we define as spatial functional network connectivity (sFNC), and changes of sFNC across a resting-state scan. We extract time-varying components from healthy controls and patients with schizophrenia to represent brain networks using independent vector analysis (IVA), which is an extension of ICA to multiple data sets and enables one to capture spatial variations. Based on mutual information among IVA components, we perform statistical analysis and Markov modeling to quantify the changes in spatial connectivity. Our experimental results suggest significantly more fluctuations in patient group and show that patients with schizophrenia have more variable patterns of spatial concordance primarily between the frontoparietal, cerebellar and temporal lobe regions. This study extends upon earlier studies showing temporal connectivity differences in similar areas on average by providing evidence that the dynamic spatial interplay between these regions is also impacted by schizophrenia.

Introduction

A very active research topic in functional magnetic resonance imaging (fMRI) studies has been the study of functional connectivity—statistical interactions among brain regions during cognitive or sensorimotor tasks, or merely from spontaneous activity during rest. Dysconnectivity or abnormal connectivity has typically been considered a hallmark of various mental disorders, especially schizophrenia (Bullmore et al., 1997; Stephan et al., 2009). Schizophrenia is still one of the most complex and heterogeneous mental disorders that impairs multiple cognitive domains including memory, attention, language, and execution function (Danielyan and Nasrallah, 2009; van Os and Kapur, 2009). Previous neuroimaging studies have found both structural and functional abnormalities in the temporal lobe, parietal cortex, and cerebellar regions for schizophrenia (Iritani, 2007). Also, evidence of dysconnectivity among a number of brain networks in schizophrenia has been reported (Jafri et al., 2008; Jones et al., 2012; Meyer-Lindenberg et al., 2001; Yu et al., 2011). Most connectivity studies use independent component analysis (ICA), a popular data-driven method, to reveal robust markers for schizophrenia biomarkers. ICA separates single-subject fMRI data into a set of maximally independent components and associated time courses (Calhoun et al., 2001a; McKeown et al., 1998). Spatial components represent temporally coherent brain networks, and functional connectivity among these networks—called functional network connectivity—is typically defined as the correlation or coherence between associated time courses (Allen et al., 2011a; Jafri et al., 2008). An advantage of using ICA-based methods for functional connectivity analysis is that no explicit prior knowledge about brain activity is required and the estimates are not biased due to selection of a seed region of interest. For multi-subject fMRI data, group ICA with temporal concatenation of data sets can be used to estimate spatial components for individual participants and thus enables group inferences (Allen et al., 2011b; Calhoun and Adalı, 2012; Calhoun et al., 2001b).

In most fMRI studies, functional connectivity is typically assumed to be stable during the entire scan. There is an increasing interest to develop approaches to examine dynamic changes in functional connectivity during the course of an experiment (Hutchison et al., 2013). For example, Sakoğlu et al. performed an ICA-based dynamic analysis on fMRI

* Corresponding author.
E-mail address: saima1@umbc.edu (S. Ma).

1053-8119/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.12.063

data acquired during both a resting state and an auditory oddball (AOD) task (Sakoğlu et al., 2010). A key motivation for such analysis is that connectivity dynamics can capture uncontrolled but reoccurring patterns of interactions among brain networks, which are not detectable through static connectivity analysis. It is especially important when the focus is intrinsic networks that are not necessarily task related, such as during resting state where diverse levels of attention and mind wandering are expected. Currently, only a few studies have focused on the dynamic changes in resting-state functional connectivity. For example, Chang and Glover performed a time-frequency coherence analysis based on wavelet transformation and found resting-state connectivity fluctuations between posterior cingulate cortex (PCC) and the networks having negative correlation with PCC (Chang and Glover, 2010); Kang et al. introduced a variable parameter regression combined with the Kalman filtering approach for resting-state dynamic patterns among eight brain networks (Kang et al., 2011); sliding-window correlation analysis was also employed on resting state data using either seed- or ICA-based methods (Allen et al., 2012; Hutchison et al., 2012; Starck et al., 2012).

The studies described above mainly focus on evaluating dynamic changes in temporal patterns. On the other hand, fluctuations related to spatial components over time are of interest as well, though there has been little work on this topic. One recent study focused on spatial changes within a single network (default mode network) using a group ICA framework (Kiviniemi et al., 2011). Analogous to functional network connectivity, we previously proposed approaches to evaluate residual component dependencies, i.e., the statistical dependencies between spatial (as opposed to temporal) component pairs that remain after blind source separation (Ma et al., 2011a,b). Such approaches are promising, as it is well known that changes in temporal connectivity patterns imply changes in spatial patterns, as shown in group ICA studies (Calhoun et al., 2008). However, the group ICA approaches involve a group-level principal component analysis (PCA), which attempts to find a common signal space for all subjects and thus introduce an averaging effect over group (Allen et al., 2011b; Esposito et al., 2005). Therefore, changes in the patterns of the spatial components may not be optimally detected using the group ICA approach. In addition, such an approach does not capitalize on the entire data set at once, and in essence, breaks the connection between the blind source separation model and the results. Thus, it is important to work with a well adapted method to capture such changes.

Independent vector analysis (IVA) is a recent extension of ICA to multiple data sets. IVA concurrently extracts independent components by fully exploiting the statistical dependence among the data sets (Anderson et al., 2012; Lee et al., 2008). In IVA, the components from a single data set are assumed to be maximally independent of each other, as in group ICA method. In contrast to group ICA, IVA also maximizes the dependence between associated components from different data sets. These associated components are conceptually regrouped into so-called source component vectors (SCVs), which cannot be achieved by separate ICA of each data set during blind source separation. IVA has shown, in most cases, superior performance in capturing variability in spatial components across individuals and groups (Dea et al., 2011; Ma et al., 2013; Michael et al., 2013). We also noted that as group variability increases, the estimation of the IVA component shows less interference from other components than that estimated by the group ICA method (Ma et al., 2013).

In this paper, we define spatial functional network connectivity (sFNC) as high-order statistical dependence among the IVA components and examine changes of sFNC over time. We employ a sliding-window approach to segment resting state fMRI data into overlapping time windows. Because IVA performs a joint separation of all time windows and subject data sets, our hypothesis is that the spatial variability will be fully captured. This is motivated by the absence of a reduction of the data to a common subspace—as needed in group ICA approaches—and is backed up with simulation results in (Dea et al., 2011; Ma et al., 2013). Hence, IVA is expected to perform much better with small records of data as it is fully taking the multivariate nature of all the available data and dependence across data sets when performing the decomposition. Based on the residual mutual information between spatial components derived from IVA decomposition, we perform statistical analysis and Markov modeling to quantify connectivity dynamics in spatial patterns.

Material and methods

Participants

Participants consisted of 10 healthy controls (HC, average age: 40 ± 11; range: 26–62; three females) and 10 patients with schizophrenia (SZ, average age: 44 ± 9; range: 25–54; two females). Patients all had chronic schizophrenia and symptoms were also assessed by positive and negative syndrome scale (PANSS). All participants were scanned during rest and they were instructed to relax with their eyes open and avoid falling into sleep. We perform two-sample *t*-tests on the age and IQ measure of subjects in the HC and SZ groups and note no significant group difference.

Image acquisition and preprocessing

A five-minute resting state scan was acquired on a Siemens 3T Allegra dedicated head scanner using single echo planar imaging with the following parameters: repetition time (TR) 1.5 s, echo time 27 ms, field of view 24 cm, 64 × 64 acquisition matrix, flip angle 70°, 3.75 × 3.75 × 4 mm^3 voxel size, 4 mm slice thickness, 1 mm gap, 29 slices, and ascending acquisition.

SPM software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) was used for fMRI data preprocessing, including realignment with INRIalign (Freire et al., 2002), spatial normalization into the standard Montreal Neurological Institute (MNI) space, resampling to 3 × 3 × 3 mm^3, resulting in 53 × 63 × 46 voxels, and smoothing with a 10 mm full width at half-maximum Gaussian kernel. In addition, to evaluate differences in motion artifacts between two groups, we performed χ^2 tests on the six estimated realignment parameters at each time point and on the absolute sum of the first three parameters and three rotational parameters. We find that for all tests, two groups have no significant differences with respect to motion artifacts ($P > 0.23$). Therefore, we believe that motion artifacts appear to have little impact on our study.

A sliding-window approach is used to segment resting state data. We first divide the original 200 time points for each subject into $L = 7$ time windows such that each contains $T = 50$ time points (window size = 75 s) and 50% of time points are overlapping between two sequential windows, as shown in Fig. 1. Then the images within each time window are reshaped into a matrix (time points by voxel numbers), denoted by a vector $\mathbf{x}^{[m,l]}$, $m = 1,\ldots,M$, $l = 1,\ldots,L$ if we consider voxels are samples for each time point, where $M = 20$ is the total number of subjects. Therefore, we perform joint blind source separation on these ML data sets, each of size $T \times V$ (where V is the number of voxels).

Independent vector analysis

We apply IVA to achieve joint blind source separation and extract spatial components from multiple subjects and different time windows concurrently. We now formulate the IVA problem for the multi-subject, multi-window fMRI analysis. Suppose each data set from the mth subject at the lth window is formed by the linear mixtures of N independent sources,

$$\mathbf{x}^{[m,l]} = \boldsymbol{A}^{[m,l]}\mathbf{s}^{[m,l]}, m = 1,\ldots,M, l = 1,\ldots,L \quad (1)$$