Journal of Neuroscience Methods 192 (2010) 207–213

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Fully exploratory network ICA (FENICA) on resting-state fMRI data

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ARTICLE INFO

Article history:
Received 19 May 2010
Received in revised form 19 July 2010
Accepted 20 July 2010

Keywords:
fMRI
ICA
Resting-state
RSN
Default mode
Group analysis

ABSTRACT

Independent component analysis (ICA) is one of the most valuable explorative methods for analyzing resting-state networks (RSNs) in fMRI, representing a data-driven approach that enables decomposition of high-dimensional data into discrete components. Extensions to a group-level suffer from the drawback of evaluating single-subject resting-state components of interest either using a predefined spatial template or via visual inspection. FENICA introduced in the context of group ICA methods is based solely on spatially consistency across subjects directly reflecting similar networks. Therefore, group data can be processed without further visual inspection of the single-subject components or the definition of a template (Schöpf et al., 2009).

In this study FENICA was applied to fMRI resting-state data from 28 healthy subjects resulting in eight group RSNs. These RSNs resemble the spatial patterns of the following previously described networks: (1) visual network, (2) default mode network, (3) sensorimotor network, (4) dorsolateral prefrontal network, (5) temporal prefrontal network, (6) basal ganglia network, (7) auditory processing network, and (8) working memory network. This novel analysis approach for identifying spatially consistent networks across a group of subjects does not require manual or template-based selection of single-subject components and, therefore, offers a truly explorative procedure of assessing RSNs.

1. Introduction

Since the seminal report of Biswal et al. (1995), spontaneous fluctuations in blood oxygen level dependent (BOLD) functional MRI (fMRI) have been repeatedly and reproducibly found to be organized in specific functional networks, and referred to as resting-state networks (RSNs) (DeLuca et al., 2006; Damoiseaux et al., 2006; Zuo et al., 2010; Meindl et al., 2010; Robinson et al., 2009). Although there is evidence for a neural basis the exact nature of these signal fluctuations is still under discussion (Raichle et al., 2001). Accordingly, methods for the detection of spontaneous fluctuations in BOLD-weighted fMRI data sets have gained considerable interest in investigational neuroimaging studies (for a short review see Auer, 2008).

Currently, different approaches for identifying patterns of coherent activity are used for the analysis of RSNs (for a review see Cole et al., 2010). The straight-forward method for hypothesis-driven RSN analysis is based on correlating the time course in a certain seed region with the time courses of all other brain voxels. Seed voxel definition is typically based on *a priori* knowledge of functional localization, i.e. a seed voxel chosen from a motor area will result in a functional connectivity map of functionally connected regions within the motor network. Several studies investigating motor, visual, auditory, and even cognitive networks have shown the applicability of this seed-based resting-state analysis (Biswal et al., 1995, 1997; Cordes et al., 2000, 2001; Fox et al., 2005). Seed voxel based methods, however, require strong *a priori* assumptions on the expected RSNs.

In contrast, data-driven or exploratory approaches do not require a specific prior model definition (Moser et al., 1999). Several types of data-driven methods such as independent component analysis (ICA) (DeLuca et al., 2006; van de Ven et al., 2004), hierarchical clustering (Golland et al., 2008; Cordes et al., 2002), and Laplacian clustering (Thirion et al., 2006), have already been applied to fMRI resting-state data on the single-subject level.

Several data-driven group analysis approaches based on ICA have been successfully introduced so far. It is, however, still under discussion whether ICA should be performed at a group-level or specific single-subject components preselected for group inferences (Damoiseaux et al., 2006; DeLuca et al., 2006; Calhoun et al., 2008; Li et al., 2007; Schöpf et al., 2010). Group ICA approaches in which single-subject data is concatenated in time have been introduced by Jafri et al. (2008) and Damoiseaux et al. (2006).

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doi:10.1016/j.jneumeth.2010.07.028

Additionally, Damoiseaux et al. (2006) used a three-dimensional tensor representing spatial, temporal and subject-specific loadings for each group component. Sorg et al. (2007) and Harrison et al. (2008) evaluated components on the single-subject level by selecting components for further group analysis via visual inspection. Greicius et al. (2003), van de Ven et al. (2004), and Calhoun et al. (2008) all based their selection of single-subject RSN components on predefined spatial templates following published RSNs. This template selection technique was also used by Garrity et al. (2007) and Greicius et al. (2007) who based their template definition on the results of previously conducted fMRI experiments.

Another evaluation approach assessing spatial consistency between component maps was recently introduced by DeLuca et al. (2006) where the spatial correlation coefficient of all components from one subject with every other subject's components is computed. In their implementation, components with correlation coefficients below 0.15 were disregarded. All component maps which survived this predefined threshold level were evaluated by visual inspection for consistent pair-wise correlations between all components of all subjects. In a second step, all resulting group maps were visually inspected for representing RSN patterns. In this group approach resulting RSNs are biased by the visual criterion used for pair-wise correlations and pattern selection.

A promising clustering-approach, not in the context of resting-state paradigms, also based on single-subject ICA has recently been introduced by Esposito et al. (2005). The algorithm introduces a complex similarity measure by taking into account spatial and temporal characteristics for clustering. As temporal RSN patterns do not imply very diverse temporal characteristics this leads to unpredictable outcomes. Furthermore, rank ordering of the extracted components is biased by visual selection of component maps.

All above selection approaches are strongly dependent on the component selection level, and true RSNs might be disregarded due to the predefined threshold level, template definition, or visual criterion. In order to overcome these limitations, we decided to use FENICA, introduced in the context of group ICA approaches (Schöpf et al., 2009), yielding activation maps without requirements for visual inspection in a statistical framework similar to that of conventional general linear model approaches. As this method allows for unbiased calculation of networks at a group-level without any requirements for visual inspection of single-subjects' components or *a priori* template definition, it provides a crucial approach of assessing RSNs.

2. Materials and methods

2.1. Subjects

Twenty-eight healthy subjects (16 females, mean age 27.3 years, SD 7.1 years) were included in the study. All subjects were informed about the aim of the study and gave their written informed consent prior to inclusion. The study was approved by the Ethics Committee of the Medical University of Vienna.

2.2. Imaging methods

Measurements were performed on a 3 Tesla Medspec S300 system (Bruker Biospin, Ettlingen, Germany) using single-shot gradient-recalled echo-planar imaging (EPI). Fourteen axial slices (6 mm thickness, 1 mm gap) with a matrix size of 64×96, FOV of 230 mm $\times$ 190 mm and TE/TR of 40/1000 ms were acquired. Slices were aligned to the connection line between anterior and posterior commissure. Subjects were instructed to relax, stay awake, and lie still, while keeping their eyes closed at all times during the 360-s resting-state scan.

2.3. Data analysis

All computations were performed on a CALLEO 321 Server equipped with two Quad-Core Intel Xeon E5450 3.0 GHz processors and 16 GB RAM (transtec GmbH, Vienna, Austria).

2.3.1. Preprocessing

Image preprocessing was performed in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) including slice-timing and motion correction, spatial normalization and spatial smoothing using a Gaussian kernel (FWHM = 9 mm). Following the recommendation of a recent study (Weissenbacher et al., 2009), we used multiple linear regression to correct data sets for residual motion and global signal changes, before applying bandpass-filtering (12-term FIR filter ($0.009 < f < 0.08$ Hz)) using IDL (RSI, USA). To correct for artifacts related to breathing, motion and heart-beat, two regions of interests (i.e., white matter and ventricles (cornu occipitale)) were defined and time courses were extracted for each subject. Time courses of both ROIs were added to a design matrix as nuisance regressors which was then used to remove corresponding physiological artifacts from the individual data sets (for further details see Weissenbacher et al., 2009). Single-subject ICA was performed using probabilistic ICA (Beckmann and Smith, 2004) as implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) version 3.05, as implemented in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The optimum number of components to be estimated for each subject was determined by using Minimum Description Length (MDL) (Rissanen, 1978).

2.3.2. Component selection

For all N subjects ICA returns N_{TOTAL} components, whereby $c_{k,m}$ is denoted as the spatial map of component number m of subject k. The number of components of a subject k is referred to as N_k. The absolute value of the correlation coefficient of component m_1 of subject k_1 and component m_2 of subject k_2 is given by

$$\mathrm{corrcoef}(c_{k_1,m_1}, c_{k_2,m_2}) = \left| \frac{\mathrm{cov}(c_{k_1,m_1}, c_{k_2,m_2})}{\sqrt{\mathrm{cov}(c_{k_1,m_1})\mathrm{cov}(c_{k_2,m_2})}} \right| \quad (1)$$

for all k_1, $k_2 \in \{1, \ldots, N\}$, $m_1 \in \{1, \ldots, N_{k_1}\}$, and $m_2 \in \{1, \ldots, N_{k_2}\}$. A correlation matrix CC of size $N_{\mathrm{TOTAL}} \times N_{\mathrm{TOTAL}}$ was calculated by spatially correlating all component maps of all N subjects.

Average maps S_ℓ are formed as the mean of c_{k_1,m_1} and c_{k_2,m_2}

$$S_\ell = \frac{c_{k_1,m_1} + c_{k_2,m_2}}{2}, \quad (2)$$

for all $k_1 \in \{1, \ldots, N\}$, $k_2 \in \{1, \ldots, N\}/\{k_1\}$, $m_1 \in \{1, \ldots, N_{k_1}\}$, and $m_2 \in \{1, \ldots, N_{k_2}\}$ resulting in N_{AVG} components, with

$$N_{\mathrm{AVG}} = ((N_{\mathrm{TOTAL}})^2 - \sum_{k=1}^{N} (N_k)^2) \cdot \frac{1}{2}.$$

Each average map S_ℓ for $\ell = 1, \ldots, N_{\mathrm{AVG}}$ is spatially correlated with all N_{TOTAL} component maps, and the map with the highest correlation within every subject was determined. Thereby we obtain one component per subject forming N_{AVG} networks, defining a network matrix N of size $N \times N_{\mathrm{AVG}}$,

$$\forall j \, \exists_1 \, \mathcal{N}(j, \ell) : \quad \max_{m=1,\ldots,N_j} [\mathrm{corrcoef}(c_{j,m}, S_\ell)], \quad (3)$$

for every $j \in \{1, \ldots, N\}$ and $\ell \in \{1, \ldots, N_{\mathrm{AVG}}\}$.

The network matrix $\mathcal{N}$ includes N_{AVG} networks that are spatially consistent across the group. A spatial equivalence level was introduced as a measure to merge spatially matching networks in order