Neuroscience Letters 498 (2011) 57–62

Contents lists available at ScienceDirect

Neuroscience Letters

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

Are posterior default-mode networks more robust than anterior default-mode networks? Evidence from resting-state fMRI data analysis

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ARTICLE INFO

Article history:
Received 31 October 2010
Received in revised form 21 April 2011
Accepted 23 April 2011

Keywords:
Default-mode networks
Resting-state networks
Functional MRI
Reproducibility
Functional connectivity
Effective connectivity
Granger causality analysis
Group independent component analysis

ABSTRACT

Intrinsic brain activity known as default-mode networks (DMNs) has been observed predominantly within the medial/superior frontal areas, anterior/posterior cingulate gyri, and precuneus using blood-oxygenation-level-dependent (BOLD) functional MRI (fMRI). Despite anecdotal evidence of distinct spatial patterns reflecting neuropsychiatric conditions in these DMNs, rigorous analysis of the characteristic traits of DMNs has been limited in previous studies. In this letter, the reproducibility and potential variability of the anterior and posterior DMNs were evaluated based on individual-level variations in effect sizes, activated areas, and causal interactions. Our results indicated that the DMNs were indeed reproducible between sessions/subjects. Region-specific traits were also observed: the posterior DMN seemed more robust to individual-level variations than the anterior DMN. The proposed analytical methods and reported findings may be useful in the development of a wide range of applications, including those involving clinical populations, which utilize the characteristic traits of DMNs.

Intrinsic activity of default-mode networks (DMNs) in the brain has been observed reproducibly in blood-oxygenation-level-dependent (BOLD) functional MRI (fMRI) studies, predominantly within the medial/superior frontal areas and anterior cingulate cortex (*i.e.,* anterior DMN or aDMN), posterior cingulate cortex (PCC) along with precuneus (*i.e.,* posterior DMN within PCC/precuneus, or $pDMN_{PCC}$), and inferior parietal lobe (IPL) (*i.e.*, $pDMN_{IPL}$) [4,24]. These DMNs have presented characteristic spatial patterns such as hyper- and hypo-activity reflecting various neuropsychiatric conditions [1,9,23]. For example, decreased regional homogeneity and loss of co-activation in the PCC and precuneus have been observed in amnestic-type mild cognitive impairment (MCI) and normal aging [1]. Furthermore, patients with Alzheimer's disease (AD) have shown decreased resting-state activity in the PCC and hippocampal regions [9]. In contrast, hyperactivity and hyperconnectivity within DMNs have been implicated in poorer working memory performance by schizophrenic patients compared to healthy controls [23].

The reproducibility of these characteristic traits of DMNs has been evaluated through group-level patterns in data from multiple sessions and subjects by adopting statistical tests such as random-effect analysis (RFX) via one-sample *t*-test [9,24]. Subsequently, ad-hoc processes such as correlation analysis have been employed to measure the reproducibility of DMNs [24]. However, because the group-level patterns are expected to present more reliable spatial patterns by reducing individual-level variations, this approach may not have fully exploited potentially significant individual-level variations in DMNs. The analysis of the reproducibility of these characteristic traits based on individual-level variations is crucial, especially for the application of DMNs to the diagnosis of various neuropsychiatric illnesses on an individual basis.

In this letter, we explicitly analyzed the reproducibility and potential variability of DMNs over multiple sessions based on individual-level variations. To do so, statistical tests such as one-way analysis-of-variance (ANOVA) and repeated measures ANOVA were deployed to investigate intra-region reproducibility across multiple sessions and inter-region variability within a single session between the aDMN, $pDMN_{PCC}$, and $pDMN_{IPL}$ using a series of characteristic performance measures. These measures included the (1) level of intrinsic neuronal activity within DMNs, (2) overlap size between individual- and group-level spatial patterns, (3) functional connectivity (FC) based on temporal correlation coefficients, and (4) effective connectivity (EC) based on causal interactions between regions-of-interest (ROIs). We hypothesized that evidence of intra-region reproducibility and inter-region variability (*i.e.,* potentially region-specific characteristics) would be observed in DMNs after applying the statistical tests to these performance measures.

Publicly available resting-state data sets comprising three sessions from a single set of subjects were used

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doi:10.1016/j.neulet.2011.04.062

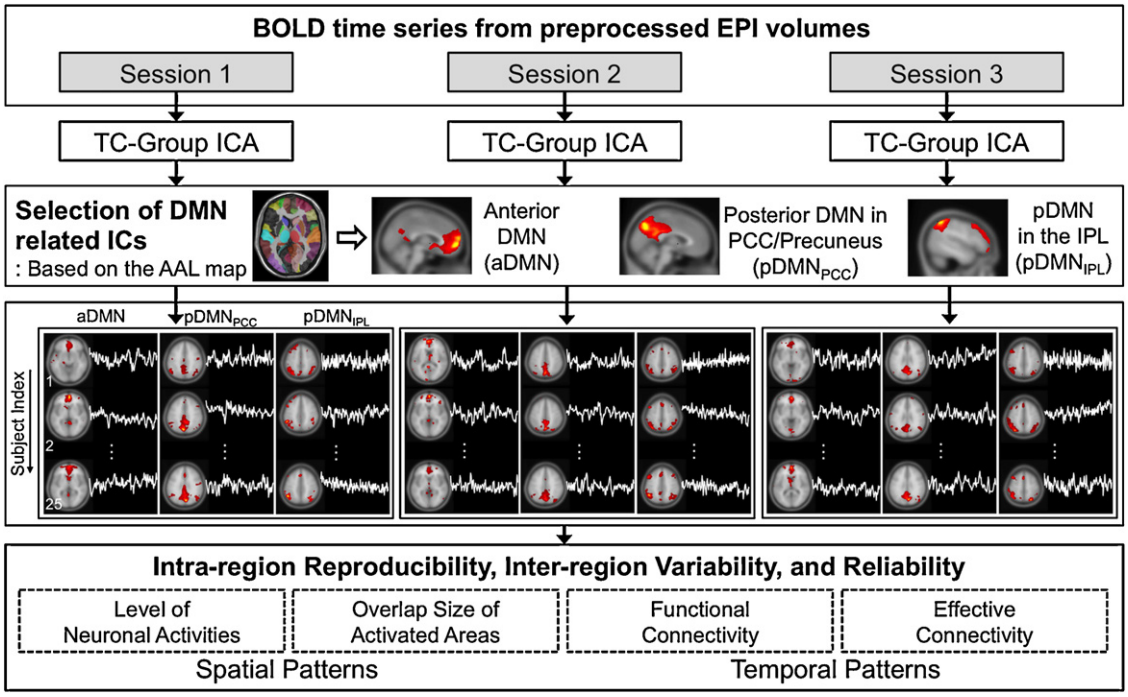

Fig. 1. Overall flow diagram. Temporally-concatenated (TC) group ICA was applied to the preprocessed EPI volumes of each session. The anterior/posterior default-mode network (DMN)-related independent components (ICs) were automatically selected based on the automated anatomical labeling (AAL) map. The resulting spatial and temporal patterns of the three DMNs (aDMN, pDMN$_{PCC}$, & pDMN$_{IPL}$) were analyzed using four performance measures to investigate intra-region reproducibility and potential inter-region variability along with corresponding reliability.

(www.nitrc.org/projects/nyu_trt). The data sets were collected from 25 subjects (15 females) during two separate visits (5–11 months apart). The second and third sessions separated by 45 min were done during the second visit. Each scan consisted of 197 echo-planar imaging (EPI) functional volumes (*i.e.*, time points) acquired every 2 s (TR/TE = 2000/25 ms; flip angle = 90°; in-plane voxels = 64 × 64; field-of-view = 192 mm; slice thickness = 3 mm; number of slices = 39). All subjects were asked to remain with their eyes open during the scan. The EPI volumes of raw fMRI data were preprocessed using the SPM2 software toolbox (www.fil.ion.ucl.ac.uk/spm) using default parameters including correction of slice timing, realignment of head movements, normalization to the MNI space with 3-mm isotropic voxel, and spatial smoothing with 6-mm full-width-at-half-maximum Gaussian kernel. Fig. 1 illustrates the overall steps to examine the characteristic traits of DMNs. The preprocessed data sets were subjected to a series of analytical steps including the application of a temporally-concatenated (TC) group independent component analysis (ICA), selection of independent components (ICs) corresponding to each of the three DMNs, and employment of performance measures.

The preprocessed EPI volumes across the 25 subjects were analyzed separately for each session using the TC group ICA (TC-GICA) implemented in the group ICA of fMRI toolbox (GIFT; icatb.sourceforge.net). The number of ICs to be estimated (*i.e.*, $n = 17$) was determined from the preprocessed data across all three sessions using the minimum description length (MDL) criterion implemented in the toolbox. Subsequently, a principal component analysis (PCA) based dimension reduction was applied to the preprocessed data before submitting them to the TC-GICA. After the ICA learning, for each resulting IC in each subject, the intensity of spatial patterns represented the level of the neuronal activity of each voxel and was normalized in voxel-wise to have a zero mean and unit variance (*i.e.*, individual *z*-scored map). Among the 17 estimated ICs, three ICs whose spatial patterns ($p < 0.01$) were significantly overlapped within the aDMN, pDMN$_{PCC}$, and pDMN$_{IPL}$ were selected using an automated anatomical labeling (AAL) map.

Using the individual *z*-scored maps of the selected ICs representing each of the three DMNs, a group-level map was obtained from the 75 *z*-scored maps of the 25 subjects over three sessions using one-sample *t*-test. The resulting group-level map was regarded as a "reference spatial template" of the corresponding DMN. The voxel with the maximum *z*-score value was subsequently identified in each reference spatial template, and the area proximal to the voxel (*i.e.*, $3 \times 3 \times 3$ voxels or $9 \times 9 \times 9\,mm^3$) was defined as an ROI for each of the three DMNs.

The levels of intrinsic neuronal activity were estimated from the mean *z*-scores in the aDMN/pDMNs. To calculate intra-region reproducibility, three sets of 25 mean *z*-scores from the 25 subjects in three sessions were analyzed using one-way ANOVA. This process aimed to determine whether the mean *z*-scores across subjects in the aDMN or pDMNs statistically differed between the three sessions. To assess inter-region variability within single session, three sets of 25 mean *z*-scores from the 25 subjects in the three DMNs were analyzed using repeated measures ANOVA with the null hypothesis that the triple sets of 25 *z*-scores from the three DMNs in a single session did not statistically differ.

Overlap of spatial patterns of activation was evaluated based on the percentage of overlap between individual-level *z*-scored maps and group-level *z*-scored map (*i.e.*, the reference spatial template). The level of FC between the DMNs of each subject in each session was evaluated using the Pearson's correlation coefficient. The linear trend in the BOLD time series that is an average of time series within the ROI from the preprocessed raw fMRI data was corrected (*i.e.*, linear detrending) to remove the potential confounding effect of low-frequency drift noise from hardware imperfections [10]. The FC level can potentially be affected by noise from various sources, such as white matter (WM), cerebro-spinal fluid (CSF), and motion artifact. Thus, in addition to the FC analysis using the detrended BOLD time series, an FC analysis based on partial correlation was