DYNAMIC DEFAULT MODE NETWORK CONNECTIVITY
DIMINISHED IN PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

Recent works have shown that, even in resting state, functional networks undergo dynamic changes over short time. In this study, we describe an approach to assess the difference in default mode network (DMN) dynamics between healthy controls (HC) and schizophrenia patients (SZ) using resting-state functional magnetic resonance imaging. Firstly, dynamic DMN was computed using a sliding time window method. Then, stability of the dynamic DMN evaluated using the spectrum of time-varying functional connectivity was compared between HC and SZ. Subsequently, the overall functional connectivity pattern and dynamic graph measures were also investigated for both groups. Results show that dynamic DMN of HC had more stable and stronger functional connectivity than that of SZ. Regarding to dynamic graph measures, SZ had lower connectivity strength, clustering coefficient, global efficiency, and local efficiency than HC. The findings suggest that dynamic functional network analysis is a promising technique for understanding schizophrenia.

Index Terms- dynamic functional network, default mode network, functional magnetic resonance imaging, schizophrenia

1. INTRODUCTION

Studies based on blood oxygenation-level dependent (BOLD) functional magnetic resonance imaging (fMRI) have revealed the presence of high temporal correlation among anatomically separated but functionally connected brain regions, which indicates functional networks [1]. Multiple functional networks have been reported using fMRI, primarily including vision network, motor and sensory network, attention network, and default mode network (DMN). DMN is the most widely studied network in resting state [2], and comprises brain regions supporting default activity of the human brain, such as attending to internal stimuli, self-reflection, or internal narrative.

Traditionally, fMRI functional networks are computed using BOLD signal of the entire scan time (5 minutes or longer), assuming that functional connectivity between brain regions is stationary. However, recent work has shown that functional networks vary over time, since cognitive processes occur on short time scales (seconds) [3]. Furthermore, temporal dynamics may be even more prominent in the resting state than in cognitive task mode due to unconstrained mental activity [4-7]. Sliding time window method [4] is a widely-used method for temporal dynamics analysis, which calculates functional connectivity on windowed periods of BOLD signal. Consequently, functional connectivity patterns under varied windows reflect the dynamic functional network. It is expected that dynamic properties of time-varying functional networks may offer significant information for understanding brain function as well as mental disease mechanisms.

Schizophrenia is a complex psychiatric disorder with altered perception, cognition, thought processes, and behaviors. Based on stationary resting-state functional networks, research works have demonstrated that schizophrenia patients present aberrant functional connectivity in multiple networks, especially DMN [8, 9]. However, to the best of our knowledge, there are still no studies to investigate schizophrenia focusing on dynamics of intra-DMN functional connectivity, although some works studied the dynamic connectivity between multiple networks including DMN [10].

This study is aimed to explore the difference in dynamic properties of default mode network (DMN) between schizophrenia patients (SZ) and healthy controls (HC) using resting-state fMRI. We investigated the following aspects: (1) whether there is difference between HC and SZ in terms of the stability of dynamic DMN; (2) whether SZ have altered functional connectivity strength compared to HC in dynamic DMN; (3) which DMN regions are relevant to aberrant functional connectivity of SZ.

2. MATERIALS AND METHODS

Resting-state fMRI from 80 HC and 80 SZ were analyzed. For each subject, given defined regions of interest (ROI), sliding time window approach was first employed to extract dynamic DMN from fMRI data. Then, the stability in dynamic DMN was evaluated via exploring spectra information of the subject-specific time-varying functional connectivity. Afterwards, dynamic functional connectivity matrixes were averaged over windows to reflect the overall connectivity pattern for each subject. Furthermore, dynamic graph measures were computed to assess the dynamic connectivity strength and stability based on each subject’s dynamic DMN. Finally, those measures including stability of functional connectivity, overall functional connectivity matrix, and dynamic graph measures were compared between HC and SZ.

2.1. fMRI data acquisition and preprocessing

Resting-state fMRI were collected from 80 HC and 80 SZ scanned on a 3-Tesla Siemens Trio scanner with a 12-channel radio frequency coil at the Mind Research Network. The functional scans were acquired using gradient echo planar imaging (EPI) with the following parameters: echo time (TE) = 29 ms, repeat time (TR) = 2 s, flip angle = 75°, slice thickness = 3.5 mm, slice gap = 1.05 mm, field of view 240 mm, matrix size = 64×64, voxel size = 3.75 mm.
Resting state scans consisted of 150 3D images. During data acquisition, subjects were asked to remain alert with eyes open and keep their head still.

An preprocessing pipeline developed at the Mind Research Network [11] was used to preprocess the fMRI data. INRIalign [12] was used to realign the images. Then the data were spatially normalized to the standard Montreal Neurological Institute (MNI) space, resampled to 3 mm × 3 mm × 3 mm voxels using the nonlinear (affine + low frequency direct cosine transform basis functions) registration implemented in SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm), and smoothed using a Gaussian kernel with a small full-width at half-maximum of 5 mm.

2.2. Dynamic DMN extraction

According to one previous work [13], 11 DMN ROI (8 mm spheres) were defined, comprising posterior cingulate cortex (PCC), anterior medial prefrontal cortex (aMPFC), dorsal medial prefrontal cortex (dMPFC), temporo-parietal junction (TPJ), left temporal cortex (LTC), temporal pole (TempP), ventral medial prefrontal cortex (vMPFC), posterior inferior parietal lobule (pIPL), retrosplenial cortex (Rsp), parahippocampal cortex (PHC), and hippocampal formation (HF) (see Fig.1). Based on these ROI, dynamic DMN was computed for each subject as follows. Firstly, we averaged the BOLD time-series among voxels within each ROI as the representative time-series of the ROI. Those representative time-series denoted by \( X_i \) for both subjects. Also, it is observed that functional network patterns corresponding to different windows from the same subject were similar to some extent. Nevertheless, it seemed that dynamic patterns varied along window. To examine if the dynamic graph measures are different over time between the two groups, the mean and standard deviation across subjects were calculated for each graph measure.

3. EXPERIMENT RESULTS

3.1. Dynamic DMN connectivity

Fig.2 displays functional connectivity matrices of dynamic DMN in five different windows for one HC and one SZ. Results revealed that functional connectivity patterns varied along time (windows) for both subjects. Also, it is observed that functional network patterns corresponding to different windows from the same subject were similar to some extent. Nevertheless, it seemed that dynamic DMN of the SZ had lower functional connectivity strengths and greater variation compared to that of the HC.
Fig.2 Functional connectivity matrixes of dynamic DMN in five different time windows (window ID=1, 30, 60, 90 and 120) for one healthy control (HC) and one schizophrenia patient (SZ), respectively. Both x-label and y-label denote the defined 11 regions of interest (ROI). The z-label denotes the window ID.

3.2. Stability of dynamic DMN
In this study, temporal stability of functional connectivity was assessed through computing the spectrum of each time-varying functional connectivity. Fig.3 shows the spectra of all paired-ROI related functional connectivity dynamic for one HC and one SZ. Results demonstrate that different functional connectivity dynamics had various spectra, and it seems that HC had relatively lower amplitude in high frequency (>0.025Hz) than SZ.

Afterwards, the low-frequency to high-frequency power ratio was used to reflect the stability of each functional connectivity dynamic. Fig.4 shows the averaged stability matrix over subjects for HC group and SZ group, which suggests that HC had slightly higher stability than SZ, though the stability pattern was similar between the two groups. The two-sample t-tests results show that functional connectivity including PCC-aMPFC, aMPFC-dMPFC, aMPFC-Rsp, TempP-Rsp, PCC-HF, dMPFC-HF, TPJ-HF, and Rsp-HF, shown in positive t-values with higher strength in HC than in SZ.

Fig.3 The spectra of dynamic DMN for one healthy control (HC) and one schizophrenia patient (SZ). Each line corresponds to the spectrum of time-varying functional connectivity for one paired-ROI.

Fig.4 Mean stability measure matrix of dynamic DMN for healthy controls (HC) and schizophrenia patients (SZ), respectively.

3.3. Connectivity strength of dynamic DMN
For each subject, the dynamic functional connectivity matrixes were averaged over windows, resulting in an overall functional connectivity matrix. Fig.5 (A) and (B) display the averaged overall functional connectivity pattern across subjects for HC and SZ, respectively. It is found that generally the DMN connectivity pattern from HC group resemble that from SZ. However, the connectivity strengths of HC group were greater compared to SZ group. The overall functional connectivity matrix between HC group and SZ group were also compared using two-sample t-tests. As seen in Fig.5(C), the significantly decreased functional connectivity in SZ includes PCC-aMPFC, PCC-dMPFC, aMPFC-dMPFC, aMPFC-Rsp, TempP-Rsp, PCC-HF, dMPFC-HF, TPJ-HF, and Rsp-HF, shown in positive t-values with higher strength in HC than in SZ.

Fig.5 (A) The averaged overall functional connectivity matrix and the network pattern thresholded by 0.35 for healthy controls (HC). (B) The averaged overall functional connectivity matrix and the network pattern thresholded by 0.35 for schizophrenia patients (SZ). (C) The two-sample t-test results and the corrected pattern (p<0.05 with family-wise error (FWE) correction) from comparing
the overall functional connectivity matrixes between HC group and SZ group.

3.4. Graph measures of dynamic DMN
Dynamic graph measures of DMN including connectivity strength, clustering coefficient, global efficiency, and local efficiency were computed for each subject, and then compared between HC group and SZ group. Fig.6 demonstrates the error bar of each dynamic graph measure for the two groups. Results reveal that SZ had lower mean for those graph measures than HC over windows.

**Fig.6 Error bar of dynamic graph measures of DMN across healthy controls (HC) and schizophrenia patients (SZ), respectively. These graph measures include connectivity strength, clustering coefficient, global efficiency, and local efficiency.**

4. DISCUSSIONS
In this study, we investigated the difference in fMRI-based dynamic DMN between HC and SZ in resting state, using stability of functional connectivity, overall functional connectivity strength, and dynamic graph measures. Results show that HC had more stable functional connectivity than SZ for DMN, primarily in PCC-aMPFC, aMPFC-LTC, dMPFC-Rsp and LTC-Rsp. Additionally, SZ had significantly decreased functional connectivity compared to HC, which include PCC-aMPFC, PCC-dMPFC, aMPFC-dMPFC, aMPFC-Rsp, TempP-Rsp, PCC-HF, dMPFC-HF, TPJ-HF, and Rsp-HF. Furthermore, dynamic DMN from SZ had lower connectivity strength, clustering coefficient, global efficiency, and local efficiency than that from HC. All these results suggest that the DMN’s functional connectivity pattern, a signature of normal mental vigilance, may be harmed by schizophrenic disease condition. In sum, our work suggests dynamic functional network analysis is able to capture the connectivity temporal variability and provide interesting insights for understanding schizophrenia.

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5. REFERENCES