Schizophrenia Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Interaction among subsystems within default mode network diminished in schizophrenia patients: A dynamic connectivity approach

Yuhui Du [a,b,*], Godfrey D. Pearlson [c,d,e], Qingbao Yu [a], Hao He [a,f], Dongdong Lin [a], Jing Sui [a,g], Lei Wu [a], Vince D. Calhoun [a,c,f]

[a] The Mind Research Network & LBERI, Albuquerque, NM, USA
[b] School of Information and Communication Engineering, North University of China, Taiyuan, China
[c] Department of Psychiatry, Yale University, New Haven, CT, USA
[d] Department of Neurobiology, Yale University, New Haven, CT, USA
[e] Olin Neuropsychiatry Research Center, Institute of Living, Hartford, CT, USA
[f] Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM, USA
[g] Brainnetome Center and National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing, China

ARTICLE INFO

Article history:
Received 2 August 2015
Received in revised form 14 November 2015
Accepted 21 November 2015
Available online xxxx

Keywords:
Dynamic functional connectivity
Default mode network
fMRI
Schizophrenia
Connectivity states

ABSTRACT

Default mode network (DMN) has been reported altered in schizophrenia (SZ) using static connectivity analysis. However, the studies on dynamic characteristics of DMN in SZ are still limited. In this work, we compare dynamic connectivity within DMN between 82 healthy controls (HC) and 82 SZ patients using resting-state fMRI. Firstly, dynamic DMN was computed using a sliding time window method for each subject. Then, the overall connectivity strengths were compared between two groups. Furthermore, we estimated functional connectivity states using K-means clustering, and then investigated group differences with respect to the connectivity strengths in states, the dwell time in each state, and the transition times between states. Finally, graph metrics of time-varying connectivity patterns and connectivity states were assessed. Results suggest that measured by the overall connectivity, HC showed stronger inter-subsystem interaction than patients. Compared to HC, patients spent more time in the states with nodes sparsely connected. For each state, SZ patients presented relatively weaker connectivity strengths mainly in inter-subsystem. Patients also exhibited lower values in averaged node strength, clustering coefficient, global efficiency, and local efficiency than HC. In summary, our findings indicate that SZ show impaired interaction among DMN subsystems, with a reduced central role for posterior cingulate cortex (PCC) and anterior medial prefrontal cortex (aMPFC) hubs as well as weaker interaction between dorsal medial prefrontal cortex (dMPFC) subsystem and medial temporal lobe (MTL) subsystem. For SZ, decreased integration of DMN may be associated with impaired ability in making self-other distinctions and coordinating present mental states with episodic decisions about future.

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 separate but functionally connected brain regions, implying brain functional networks (Sporns, 2014). Multiple functional networks have been detected using fMRI, mainly including vision network, motor and sensory network, attention network, and default mode network (DMN). DMN, which is thought to underlie processes of internal stimuli, self-reflection, or internal narrative (Andrews-Hanna, 2012; Andrews-Hanna et al., 2014; Buckner, 2013), is one of the most widely studied functional networks using resting-state fMRI.

Traditionally, functional networks derived from fMRI data are computed using the BOLD signal of the entire scan time (5 min or longer), assuming that functional connectivity among brain regions is static. However, recent work has shown temporal dynamics of functional connectivity (Calhoun et al., 2014). This dynamic functional connectivity, which varies over a time frame of seconds, may be highly related to unconstrained mental activity in the resting state (Allen et al., 2014; Hutchison et al., 2013; Zalesky et al., 2014). A widely applied method for temporal dynamics analysis is the sliding time window method (Di and Biswal, 2015; Hutchison et al., 2013; Sakoglu et al., 2010). Using the method, the entire BOLD signal is divided into periods of windows, which are then used to construct window based brain functional connectivity. The derived time-varying functional connectivity patterns under varied windows reflect the dynamics of brain functional network

* Corresponding author at: The Mind Research Network, 1101 Yale Blvd NE, Albuquerque, NM 87106, USA.
E-mail address: ydu@mrn.org (Y. Du).

http://dx.doi.org/10.1016/j.schres.2015.11.021

and thereby are expected to facilitate our understanding of mechanism underlying the mental disease.

Schizophrenia (SZ) is a complex psychiatric disorder with altered perception, cognition, thought processes, and behaviors, for which biomarkers are still lacking. Brain-imaging studies suggest that SZ is a disorder with altered brain structure and function (Fitzsimmons et al., 2013; Skudlarski et al., 2010). Previous studies using static connectivity analysis methods have demonstrated that SZ patients exhibited dysfunction in multiple networks (Baker et al., 2014; Calhoun et al., 2009; Du et al., 2015; Lynall et al., 2010; Repovs et al., 2011; Rotarska-Jagiela et al., 2010), especially in DMN (Broyd et al., 2009; Garrity et al., 2007; Meda et al., 2014; Tang et al., 2013; Whitfield-Gabrieli et al., 2009). Since DMN has been found to be involved in cognitive and social processing, symptoms of SZ relating to deficits in social cognition function may be associated with the impairment of DMN. Disrupted DMN with reduced functional connectivity among network nodes has been observed in SZ patients (Bastos-Leite et al., 2015; Bluhm et al., 2007; Bluhm et al., 2009; Camchong et al., 2011; Jang et al., 2011), although inconsistent findings exist (Whitfield-Gabrieli et al., 2009; Zhou et al., 2007). Furthermore, there is evidence (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014; Buckner et al., 2008; Uddin et al., 2009), which supports that brain regions within DMN contribute to specialized functions underlying subsystems. Some studies (Chang et al., 2014; Dodell-Feder et al., 2014) have reported reduced activation within subsystems of DMN in SZ patients. Using independent component analysis (ICA), Garrity et al. (Garrity et al., 2007) revealed impaired interaction between anterior and posterior regions of DMN in SZ patients. A recent study (Bastos-Leite et al., 2015) analyzed effective connectivity within DMN, and observed relatively weaker connectivity between anterior frontal and posterior cingulate in patients with first-episode SZ. However, the studies on alteration of connectivities among different subsystems of DMN are still limited. Moreover, most previous work used a static analysis method to extract functional networks. Recently, some studies (Damaraju et al., 2014; Rashid et al., 2014; Yu et al., 2015) compared SZ patients and healthy controls using dynamic functional network connectivity (dFNC), and observed abnormal interaction among networks that include DMN. The dFNC (Allen et al., 2014) was estimated using correlation between windowed time courses of networks which are extracted by ICA. However, to the best of our knowledge, no studies have focused on dynamic connectivity within DMN in SZ, especially the interaction among DMN subsystems. It is important to investigate the aberrance in SZ with respect to inter-subsystem dynamic connectivity of DMN, due to that DMN subsystems contribute to different cognition functions.

The aim of this study is to evaluate the difference of dynamic connectivity within DMN between healthy controls (HC) and SZ patients using resting-state fMRI. Our major goals involve the following aspects: (1) whether SZ patients show altered functional connectivity strengths compared to HC in dynamic DMN, and which DMN regions or subsystems are disrupted in SZ; (2) whether dynamic DMN of these two groups undergoes different functional connectivity states. And if so, what kind of aberrance occurs in connectivity states of SZ patients; and finally, (3) whether the graph theory based metrics in terms of dynamic DMN are different between the two groups.

2. Materials and methods

2.1. fMRI data acquisition and preprocessing

Resting-state fMRI was collected from 82 HC (age: 37.7 ± 10.8, 19 females) and 82 SZ patients (age: 38.0 ± 14.0, 17 females) scanned on a 3-Tesla Siemens Trio scanner with a 12-channel radio frequency coil at the Mind Research Network. All participants provided written, informed consent according to the Mind Research Network institutional guidelines. Age of the two groups showed no significant group difference (two-sample t-test, $p = 0.87$). SZ was diagnosed according to DSMIV-TR criteria on the basis of a structured clinical interview. Patients were assessed with the positive and negative syndrome scale (PANSS): positive score: 15.3 ± 4.8, range 7–29; negative score: 15.1 ± 5.3, range 8–29. All patients were prescribed a variety of psychoactive medications. Additional information of these participants can be found in (Yu et al., 2015). 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 × 3.75 mm × 4.55 mm. Resting state scans consisted of 150 whole brain images. During data acquisition, subjects were asked to remain alert with eyes open and keep their head still.

A preprocessing pipeline developed at the Mind Research Network (Bockholt et al., 2010) was used to preprocess the fMRI data. INRIalign (Freire et al., 2002) 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. Computation of dynamic connectivity within DMN

According to previous work (Andrews-Hanna et al., 2010; Dodell-Feder et al., 2014; Kucyi and Davis, 2014), 11 regions of interest (ROIs) were defined using 8 mm radii spheres (see Fig. 1 and Table 1). These ROIs comprise posterior cingulate cortex (PCC), anterior medial prefrontal cortex (aMPFC), dorsal medial prefrontal cortex (dMPFC), temporo-parietal junction (TPJ), lateral 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). Similar to previous work (Andrews-Hanna et al., 2010; Dodell-Feder et al., 2014), only left-lateralized and midline regions were applied in this study in order to prevent biasing the connectivity structure toward the strong correlations between the mirrored ROIs. Andrews-Hanna et al. (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014) have suggested that DMN can be partitioned into two core hubs (PCC and aMPFC) and two additional subsystems that include dMPFC subsystem and medial temporal lobe (MTL) subsystem. The two core hubs contribute to constructing personal meaning from salient information. The dMPFC subsystem including dMPFC, TPJ, LTC, and TempP is engaged in thoughts about the present states of one's self and/or other people. The MTL subsystem, comprising vMPFC, pIPL, Rsp, PHC, and HF, has been shown to be activated when decisions involve constructing a mental scene based on memory in some work (Andrews-Hanna et al., 2010), and is also reported to be engaged preferentially when the participants make episodic decisions about their future (Andrews-Hanna et al., 2014; Li et al., 2014; Schacter and Addis, 2007; Supek and Aine, 2014). Evidence (Supek and Aine, 2014) suggests that the MTL subsystem is related to the act of simulating the future using mnemonic imagery-based processes rather than to temporal aspects of the future per se. Both dMPFC and MTL subsystems were reported to be strongly correlated with the two hubs when people make self-relevant affective decisions. For simplicity, we also referred to the two core hubs as subsystems hereinafter.

Based on these ROIs, dynamic connectivities within DMN were computed for each subject as follows. Firstly, we averaged the BOLD time-series of voxels within each ROI as the representative signal of the ROI. Those representative signals denoted by X_i $(i = 1, 2, \cdots, 11)$ were then processed via regressing head motion, detrending, and band pass filtering (0.01 Hz–0.08 Hz). Next, each X_i was segmented into windowed time-series $Y_{i,w}$ $(w = 1, 2, \cdots, n)$, where n is the number of windows and w is the window ID. In this paper, a tapered window

Please cite this article as: Du, Y., et al., Interaction among subsystems within default mode network diminished in schizophrenia patients: A dynamic connectivity approach, Schizophr. Res. (2015), http://dx.doi.org/10.1016/j.schres.2015.11.021