BRAIN RESEARCH 1562 (2014) 87–99

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Altered default mode and fronto-parietal network subsystems in patients with schizophrenia and their unaffected siblings

Xiao Chang[a,1], Hui Shen[b,1], Lubin Wang[b], Zhening Liu[c], Wei Xin[a], Dewen Hu[b,*], Danmin Miao[a,*]

[a]Department of Psychology, Fourth Military Medical University, Xi'an, Shannxi 710032, China
[b]College of Mechatronics and Automation, National University of Defense Technology, Changsha, Hunan 410073, China
[c]Mental Health Institute, Second Xiangya Hospital, Central South University, Changsha, Hunan, China

ARTICLE INFO

Article history:
Accepted 17 March 2014
Available online 25 March 2014

Keywords:
FMRI
Schizophrenia
Genetic risk
Subsystem
Default mode network
Fronto-parietal network

ABSTRACT

The complex symptoms of schizophrenia have recently been linked to disrupted neural circuits and corresponding malfunction of two higher-order intrinsic brain networks: The default mode network (DMN) and the fronto-parietal network (FPN). These networks are both functionally heterogeneous and consist of multiple subsystems. However, the extent to which these subsystems make differential contributions to disorder symptoms and to what degree such abnormalities occur in unaffected siblings have yet to be clarified. We used resting-state functional MRI (rs-fMRI) to examine group differences in intra- and inter-connectivity of subsystems within the two neural networks, across a sample of patients with schizophrenia ($n=24$), their unaffected siblings ($n=25$), and healthy controls ($n=22$). We used group independent component analysis (gICA) to identify four network subsystems, including anterior and posterior portions of the DMN (aDMN, pDMN) as well as left- and right-lateralized portions of the FPN (lFPN, rFPN). Intra-connectivity is defined as neural coherence within a subsystem whereas inter-connectivity refers to functional connectivity between subsystems. In terms of intra-connectivity, patients and siblings shared dysconnection within the aDMN and two FPN subsystems, while both groups preserved connectivity within the pDMN. In terms of inter-connectivity, all groups exhibited positive connections between FPN and DMN subsystems, with patients having even stronger interaction between rFPN and aDMN than the controls, a feature that may underlie their psychotic symptoms. Our results implicate that DMN subsystems exhibit different liabilities to the disease risk while FPN subsystems demonstrate distinct inter-connectivity alterations. These dissociating manners between network subsystems explicitly suggest their differentiating roles to the disease susceptibility and manifestation.

*Corresponding authors.
E-mail addresses: dwhu@nudt.edu.cn (D. Hu), psychmiao@163.com (D. Miao).
[1]These authors contributed equally to this paper.

http://dx.doi.org/10.1016/j.brainres.2014.03.024
0006-8993/

1. Introduction

Schizophrenia is a complicated syndrome associated with the malfunction of multiple large-scale brain networks (Bullmore et al., 1997; Friston, 1999; Selemon and Goldman-Rakic, 1999; Stephan et al., 2009). Some of these brain networks appear to be crucial for both daily functioning and disease pathology (Broyd et al., 2009; Menon, 2011; Khadka et al., 2013). In particular, two higher-order functional networks have received particular attention for their potential relevance to schizophrenia (Williamson, 2007; Menon, 2011). The first of these is the default mode network (DMN), with key nodes in the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), precuneus cortex and bilateral angular gyri (AG). It often shows deactivation during externally attention demanding tasks while increases activity during unconstrained thought (Binder et al., 1999; Mason et al., 2007; McKiernan et al., 2006), introspection (Svoboda et al., 2006), and self-related processing (Lin et al., 2011). The other network is fronto-parietal network (FPN), mainly encompassing bilateral dorsolateral prefrontal cortex (DLPFC) and inferior parietal lobule (IPL). This network is often evoked by various cognitive tasks (Fox et al., 2005; Dosenbach et al., 2006, 2007; Fassbender et al., 2006; Vincent et al., 2008; Cole et al., 2013). Although earlier investigations suggested a striking antagonistic relationship between the two networks, more recent studies have found evidence for their flexible, dynamic engagement according to the task requirement (Fornito et al., 2012; De Pisapia et al., 2012; Cocchi et al., 2013; Spreng et al., 2013). DMN and FPN abnormalities have been suggested to underlie many clinical features of schizophrenia (Greicius et al., 2003; Williamson, 2007; Buckner et al., 2008; Broyd et al., 2009). For example, the DMN is thought to be engaged in self-relevant internal information processing (Raichle and Snyder, 2007). Failure of this function could lead an individual to mistakenly recognize internally generated thoughts as exogenous (Frith, 1995). In addition, multiple executive functions subserved by the FPN are impaired even years before illness onset, including working memory, sustained attention, and verbal declarative memory (Torrey, 2007; Woo et al., 2008; Yildiz et al., 2011). Considering the crucial information process and the potential pathology involved in these two networks, we are motivated to investigate intrinsic connectivity within and between them.

Apart from numerous investigations examining the large-scale brain network as a whole, some studies have identified functional differentiation within already defined networks, particularly the DMN and the FPN, which have been characterized as heterogeneous systems (Andrews-Hanna et al., 2010; Buckner et al., 2008; Hassabis et al., 2007; Seeley et al., 2007; Uddin et al., 2009, 2010; Leech et al., 2011). For example, areas in anterior portion of DMN (aDMN) are involved in mentalizing (Gilbert et al., 2006), social cognition (Blakemore, 2008), and self-referential processing (D'Argembeau et al., 2005), whereas posterior DMN (pDMN) regions are implicated in episodic memory retrieval (Greicius et al., 2003) and gathering environmental information (Raichle and Snyder, 2007). Leech et al. (2011) reported that the PCC (a central hub in DMN) demonstrates dissociating functions between its ventral and dorsal areas. The dorsal PCC may serve as an interface between attention competitive networks. Investigations also suggest different contributions from network subsystems to the pathology of schizophrenia, with the aDMN being implicated in particular. Dost Öngür et al. (2010) found that schizophrenic and bipolar patients shared reduced DMN connectivity in MPFC during a resting state. Camchong et al. (2011) reported that functional and anatomical connectivity abnormalities converge on aDMN regions in patients with schizophrenia. Meanwhile, functional dysconnection of this area showed correlations with patients' clinical symptom and cognitive ability (attention and concentration). Dysconnection in FPN also plays an important role in the neural mechanism of schizophrenia (Tu et al., 2013; Roiser et al., 2013; Anticevic et al., 2012). Within this network, patients showed decreased separation between two lateralized FPN subsystems, with the right portions of FPN (rFPN) laterality index correlating with disorganization symptom severity (Rotarska-Jagiela et al., 2010). Evidence is beginning to imply that both DMN and FPN subsystems play differential roles in schizophrenia symptomatology, suggesting that it would be helpful to examine functional connectivity at the subsystem level.

To further elucidate the degree to which connectivity alterations may reflect the influence of disease risk or illness manifestation, we included patients' unaffected siblings, who share half of susceptibility genes with the patients. Although siblings of patients with schizophrenia show largely preserved abilities in sensory, motor, emotional, and social interaction domains, studies have detected mild cognitive deficits in these individuals (Sitskoorn et al., 2004). Imaging studies suggested that disruption in specific areas of FPN may underlie these behavior anomalies. In a review of fMRI studies about patients' relatives, MacDonald et al. (2009) found that the most consistent task-based activation abnormities are in right ventral prefrontal cortex and right parietal cortex. Rasetti et al. (2011) reported a susceptible gene (ZNF804A) modulate right DLPFC coupling with the hippocampus in siblings and patients. Abnormalities in regions of DMN have also been identified in patients' relatives. Two studies reported abruptions in the aDMN areas while one study found both anterior and posterior DMN anomalies (Whalley et al., 2005; Whitfield-Gabrieli et al., 2009; Jang et al., 2011). To comprehensively explore specific contribution from DMN and FPN areas to the disease pathology, further investigations are still needed.

The present study investigated resting-state functional connectivity within and between DMN and FPN subsystems, in patients with schizophrenia, their unaffected siblings, and healthy controls. Since there is currently no consensus as to the exact number of subsystems within DMN and FPN, we used group independent component analysis (gICA), a multivariate data-driven method, instead of the seed-based method to construct large-scale intrinsic networks (Calhoun et al., 2001; Jafri et al., 2008). A component derived from the gICA consists of voxels sharing coherent neural activity, representing a functional entity (i.e. a network subsystem in our study). Voxel-wise z-value reflects intra-connectivity strength of individual voxel to that subsystem (Sorg et al., 2013). We first assessed intra-connectivity differences by comparing spatial extend and intensity of each subsystem map across the three groups. Then we defined inter-connectivity as Pearson correlation between subsystem time-courses. Within- and between-group statistical analyses were performed on all inter-connections between subsystems. Taken together, we aimed to comprehensively examine intra- and inter-connectivity alterations in DMN and FPN at the subsystem level, in both patients and their unaffected siblings.