



Functional asymmetry of thalamocortical networks in subjects at ultra-high risk for psychosis and first-episode schizophrenia

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Abstract

Disrupted functional asymmetry has been implicated in schizophrenia. However, it remains unknown whether disrupted functional asymmetry originates from intra-hemispheric and/or inter-hemispheric functional connectivity (FC) in the patients, and whether it starts at very early stage of psychosis. Seventy-six patients with first-episode, drug-naïve schizophrenia, 74 subjects at ultra-high risk for psychosis (UHR), and 71 healthy controls underwent resting-state functional magnetic resonance imaging. The ‘Parameter of asymmetry’ (PAS) metric was calculated and support vector machine (SVM) classification analysis was applied to analyze the data. Compared with healthy controls, patients exhibited decreased PAS in the left thalamus/pallidum, right hippocampus/parahippocampus, right inferior frontal gyrus/insula, right thalamus, and left inferior parietal lobule, and increased PAS in the left calcarine, right superior occipital gyrus/middle occipital gyrus, and right precentral gyrus/postcentral gyrus. By contrast, UHR subjects showed decreased PAS in the left thalamus relative to healthy

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controls. A negative correlation was observed between decreased PAS in the right hippocampus/parahippocampus and Brief Visuospatial Memory Test-Revised (BVM-T-R) scores in the patients ($r = -0.364$, $p = 0.002$). Moreover, the PAS values in the left thalamus could discriminate the patients/UHR subjects from the controls with acceptable sensitivities (68.42%/81.08%). First-episode patients and UHR subjects shared decreased PAS in the left thalamus. This observed pattern of functional asymmetry highlights the involvement of the thalamus in the pathophysiology of psychosis and may also be applied as a very early marker for psychosis.

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1. Introduction

The pathophysiology of schizophrenia is hypothesized to include abnormal functional connectivity (FC) between the thalamus and cortex, which topographically organizes as the thalamocortical networks (Swerdlow, 2010; Woodward et al., 2012). Parallel circuits link specific thalamic nuclei to distinct regions in the cerebral cortex (Alexander et al., 1986; Haber, 2003). For example, the prefrontal cortex links preferentially to the anterior and dorsomedial thalamus (Alexander et al., 1986). Thalamocortical dysfunction has been reported by several structural and functional imaging studies (Glahn et al., 2008; Minzenberg et al., 2009; Shenton et al., 2001; Welsh et al., 2010), which may account for clinical and cognitive symptoms observed in schizophrenia (Andreasen et al., 1998).

Healthy human subjects are known to demonstrate several significant functional asymmetries. For example, the right visual hemisphere is more specialized for low spatial frequencies, whereas the left hemisphere prefers to treat high spatial frequencies (Sergent and Bindra, 1981). However, the pattern of normal asymmetry in healthy subjects is disrupted in schizophrenia (Ke et al., 2010). Several investigations indicate that schizophrenia may be associated with abnormal development of the left hemispheric dominance for language (Artiges et al., 2000; Dollfus et al., 2005; Sommer et al., 2001b). Some visual task-related functional magnetic resonance imaging (fMRI) studies have observed the right hemispheric asymmetry in patients with schizophrenia to process sensory information (Gur and Chin, 1999; Heckers et al., 2002). Furthermore, right-sided pathophysiology has been revealed in schizophrenia by diffusion tensor imaging (DTI) studies (Federspiel et al., 2006; Guo et al., 2012; Matsumoto et al., 2001). In addition, decreased inter-hemispheric FC in patients with schizophrenia and their unaffected siblings have been observed by our group and others (Guo et al., 2014a, 2018, 2014b; Hoptman et al., 2012; Liu et al., 2018). As a result, the lack of normal asymmetry may be related to damage to intrinsic neural circuits (Malaspina et al., 2004; Sears et al., 2000). However, the importance of damage to the functional asymmetry of specific networks (for example, the thalamocortical networks), remains unclear. Moreover, the two hemispheres have functional interaction via the corpus callosum (Lamantia and Rakic, 1990), and thus a single brain region has FCs associated with both intra-hemispheric and inter-hemispheric connections. It is also unknown whether disrupted asymmetry of the thalamocortical networks in schizophrenia results from intra-hemispheric or inter-hemispheric FCs.

Furthermore, schizophrenia is considered as a neurodevelopmental disorder (Fair et al., 2010), and thus the question is raised whether disrupted functional asymmetry of the thalamocortical networks starts at very early stage of psychosis. To answer this question, it is critical to recruit a group of subjects at ultra-high risk for psychosis (UHR). Compared with patients with schizophrenia, UHR subjects exhibit similar but more attenuated abnormalities, including clinical symptoms (Yung et al., 1996), cognitive impairments (Fusar-Poli et al., 2012; Hur et al., 2012; Kim et al., 2011), structural (Han et al., 2012; Jung et al., 2012, 2011; Smieskova et al., 2010) and functional changes (Choi et al., 2012; Fusar-Poli et al., 2010; Li et al., 2018; Wang et al., 2016a, 2016b). Moreover, UHR subjects are related to an increased risk of transferring to frank psychosis within two years (Cannon et al., 2008; Yung et al., 2008). Therefore, it is important to identify early biomarkers that can be applied to discriminate UHR subjects from healthy controls (Peters et al., 2009).

Previous studies have employed independent component analysis (ICA) and resting-state FC strength to assess functional asymmetry (Guo et al., 2018, 2014b; Sommer et al., 2001a). However, the human brain exhibits both inter-hemispheric and intra-hemispheric interactions when reacting to a stimulus. Hence, both inter-hemispheric and intra-hemispheric FC can be used to assess brain functional asymmetry. Previously, Mueller et al. proposed an 'autonomy index' (AI) to assess brain functional asymmetry by counting the numbers of abnormal voxels in each hemisphere (Mueller et al., 2015). While the AI can assess functional asymmetry, it neglects the actual observed magnitude of the correlation coefficients of the abnormal voxels, which is an important characteristic of functional asymmetry. By contrast, we proposed another analysis metric, the 'parameter of asymmetry' (PAS), to assess correlation coefficients of abnormal voxels in a previous study (Zhu et al., 2018). PAS is a voxel-wise method which is not affected by pre-selected regions of interest (ROIs) or thresholding. In addition, the potential confounding effects of ROI-selection bias and structural asymmetry can be minimized.

Given this background, a resting-state fMRI study was conducted in drug-naïve, first-episode schizophrenia patients (FEPs), UHR subjects and healthy controls. FEPs and UHR subjects were recruited in order to limit confounding effects caused by long illness duration and medication use, and to document a progressive aspect in psychosis onset. The images were analyzed by using a voxel-wise whole-brain FC method. FC was further divided into intra-hemispheric and inter-hemispheric FCs to determine the magnitude of functional asymmetry observed using the PAS method. Based

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