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Schizophrenia and the brain's control network: Aberrant within- and between-network connectivity of the frontoparietal network in schizophrenia

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ABSTRACT

The deficit of executive control is a core feature of schizophrenia, and as such, it provides hints for the neural signature of this devastating mental illness. The frontoparietal network (FPN) is a newly defined network important for various tasks requiring executive control. This study aims to investigate both the within- and between-network connectivity of the FPN in schizophrenia using functional connectivity MRI (fcMRI). Thirty-six subjects with schizophrenia and thirty-six healthy controls were enrolled. Each subject received resting fMRI scanning, clinical evaluations and cognitive examinations. Twenty-two regions of interest (ROIs) in the key hubs of the FPN were defined according to the functional connectivity map of the left and right dorsolateral prefrontal cortex (dlPFC) and included the bilateral frontal pole, inferior parietal lobe (IPL), insula, dorsomedial prefrontal cortex (dmPFC), middle cingulate cortex (mCC), precuneus, caudate, thalamus and cerebellum. Between-group comparisons were conducted using both multiple ROI-based and brain-wise analyses. The ROI-based analysis revealed that the schizophrenic participants were associated with a prominent cortico–subcortical disconnection within the FPN. Further brain-wise analyses demonstrated that the schizophrenia patients showed increased functional connectivity between several ROIs in the FPN and regions belonging to the primary sensory processing or default mode networks. These results indicated that schizophrenia is associated with both within- and between-network dysconnectivity of the FPN. Together with our previous findings of the cortico–striatal disconnection of the cingulo-opercular network, we suggest that the brain's control networks may play an important role in the neural mechanisms of schizophrenia.

1. Introduction

The lack or loss of executive control is a core feature of schizophrenia and may elucidate the underlying neural substrate of this devastating disease. Early studies largely attributed the deficit to the prefrontal cortex (PFC), especially the dorsolateral prefrontal cortex (dlPFC) (Weinberger et al., 1986; Goldman-Rakic and Selemon, 1997). A recent meta-analysis (Minzenberg et al., 2009) of 41 fMRI studies on executive function demonstrated that patients with schizophrenia showed altered neural activity, with deficits in the dlPFC, anterior cingulate cortex, and mediodorsal nucleus of the thalamus. Increases in activity were evident in other PFC areas, the precentral gyrus, the superior temporal gyrus and the visual areas. The complex pattern of hyper- and hypo-activation indicated that researchers should consider the whole network of regions involved in executive control tasks when making inferences about the neural substrates of schizophrenia, and furthermore, that a direct evaluation of these networks may provide a more direct way to evaluate the neural mechanisms of the deficits associated with schizophrenic behavior. Recent developments in functional connectivity MRI (fcMRI) suggested that the tasks requiring executive control may recruit the same set of large-scale networks important for cognitive control. These networks are referred to as the brain's control networks (Dosenbach et al., 2007, 2008) as opposed to the brain's default network (DMN) (Raichle et al., 2001; Greicius et al., 2003), which was usually less active during these tasks. Using the functional activations during the executive task as the regions of interest (ROIs), the resting fcMRI analysis from 2 independent groups (Dosenbach et al., 2007; Seeley et al., 2007) consistently found that the activation can be grouped into 2 networks: (1) the cingulo-opercular network (CON) and (2) frontoparietal network (FPN). Dosenbach et al. (2007) suggested that the FPN operates on a shorter time scale than the CON and provides a trial-by-trial modulation of brain activity for the duration of the task blocks. Seeley et al. (2007) used slightly different nomenclatures for the network, referring to it as the executive control

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network (ECN), and demonstrated that the functional connectivity within the network correlated with performance on the trail making test, which assesses cognitive flexibility. A later fcMRI study (Vincent et al., 2008) performed a detailed analysis of the frontoparietal control system and found that it is located between the default network and dorsal attention system in frontal and parietal lobes and that this system may play an optimal role, as it is positioned to integrate information from these two opposing brain systems. This critical role was supported by a recent fMRI study (Spreng et al., 2010) that showed that the FPN may flexibly couple with the default and dorsal attention networks according to different task domains, thus supporting goal-directed cognitive processes.

To date, most of the fcMRI studies on schizophrenia focused on the DMN (Bluhm et al., 2007; Garrity et al., 2007; Whitfield-Gabrieli et al., 2009); thus, seed-based functional connectivity analyses regarding the FPN are limited. Zhou et al. (2007) were the first to use fcMRI to investigate the functional connectivity of bilateral dorsolateral prefrontal cortex (dlPFC) (an important hubs of the FPN) in first episode patients with schizophrenia and showed reduced functional connectivity to the parietal lobe, posterior cingulate cortex, thalamus, and striatum. An fcMRI study (Repovs et al., 2011) investigated both the within- and between-network connectivity of several large-scale networks, including the FPN, and did not reveal any significant within-network disconnections. However, the functional connectivity between the FPN and CON or cerebellar network was reduced. In contrast, another study (Woodward et al., 2011) used a seed in the dlPFC to derive the FPN and found that the averaged functional connectivity within several important hubs of the FPN was significantly reduced in patients diagnosed with schizophrenia. Importantly, this study also analyzed the mean functional connectivity within the DMN and did not find reduced FC in schizophrenic patients, thus providing evidence that the FPN may have greater involvement in those with schizophrenia. These studies provided preliminary evidence for disconnections in the FPN in schizophrenia patients, but a detailed analysis of region-specific disconnections in the FPN has not been available until now.

This study aimed to use fcMRI to conduct a detailed functional connectivity analysis of the FPN in schizophrenia patients and test the hypothesis that schizophrenia is associated with a functional disconnect within the FPN. To estimate the hub regions of the FPN without bias, we defined 22 regions of interest (ROIs) in an independent data set of 100 subjects. Between-group comparisons were performed with two methods. First, the functional connectivity for each pair of ROIs was calculated and compared between groups to investigate the within-network disconnect of the FPN in schizophrenia patients. Second, we derived functional connectivity maps for each ROI for every participant, and between-group, brain-wise comparisons were conducted to address any significant differences in functional connectivity between these hub regions, as previous fcMRI studies have provided evidence for the importance of aberrant interactions between different large-scale networks in schizophrenia patients (Repovs et al., 2011). The analysis detected both within- and between-network disconnections.

2. Materials and methods

2.1. Participants

The schizophrenia group comprised thirty-six outpatients and inpatients from the Taipei Veterans General Hospital in Taiwan (Table 1). Structured clinical interviews based on the DSM-IV (First et al., 1997) confirmed the diagnosis. The patients were also evaluated using the Mini-International Neuropsychiatric Inventory Plus (MINI) (Sheehan et al., 1998). The participants were screened to exclude those with the following conditions: 1) substance abuse or dependence issues during the preceding six months; 2) a history of head injuries that resulted in sustained loss of consciousness, cognitive sequelae, or both; and 3) neurologic illness or any other disorder that affects cerebral metabolism. With the exception of one non-medicated individual, all patients used a variety of atypical antipsychotics prior to participating in the experiment, including paliperidone ER (N = 14), aripiprazole (Abilify, N = 6), risperidone (N = 4), olanzapine (N = 3), Solian (N = 2), Seroquel (N = 2), Haldol (N = 2), clozapine (N = 2) and Geodone (N = 1). Thirty-six age-, gender-, and handedness-matched healthy controls were recruited via advertisements. An experienced psychiatrist administered the MINI to screen and exclude candidates with major psychiatric illnesses. In addition, candidates with histories of Axis-I disorders, including schizophrenia, major depression or bipolar disorder in their first-degree relatives were excluded. The clinical status of the schizophrenia patients was characterized using the Positive and

Table 1
Means, standard deviations, and group comparisons of demographic data, rating scale scores and neuropsychological performance for healthy and patients.

Subjects Characteristics	SZ patients (n = 36)	Healthy controls (n = 36)	*t*	P
Age (years)	32.9 ± 7.8	32.9 ± 7.0	−0.03	.975
Sex	19 M/17 F	16 M/20 F	$\chi 2 = 0.50$	.479
Education level	14.6 ± 1.5	15.1 ± 1.7	−1.2	.232
Handedness	34R/2 L	36R/0 L	$\chi 2 = 2.1$	.151
Age at onset	23.3 ± 5.4			
Length of illness (years)	10.0 ± 7.3			
PANSS total	60.4. ± 12.1			
Positive subscale	14.6 ± 4.4			
Negative subscale	15.3 ± 4.9			
General psychopathology	30.5 ± 6.1			
Neuropsychological test				
Color Trail Test (CTT)				
Trail 1 time	48.9 ± 16.3	35.65 ± 9.7	4.1	.000*
Trail 2 time	92.1 ± 32.1	65.16 ± 11.6	4.7	.000*
Interference index	0.96 ± 0.52	0.91 ± 0.5	0.3	.705
Working memory(1-back)				
Mean reaction time	626.5 ± 148.7	564.68 ± 128.9	1.8	.064
Correct	13.8 ± 1.8	14.89 ± 0.3	−3.7	.000*
Working memory(2-back)				
Mean reaction time	856.2 ± 171.1	641.54 ± 164.9	5.4	.000*
Correct	10.1 ± 3.9	13.47 ± 2.3	−4.5	.000*

SZ = schizophrenia; M = Male; F = Female; PANSS = Positive and Negative Syndrome Scale.
* $P < 0.05$.