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Network-specific cortico-thalamic dysconnection in schizophrenia revealed by intrinsic functional connectivity analyses

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ABSTRACT

Background: Cortico-thalamic connections are thought to be abnormal in schizophrenia due to their important roles in sensory relay and higher cognitive control, both of which are affected by this devastating illness. This study tested the cortico-thalamic dysconnection hypothesis in schizophrenia and further explored cortico-thalamic network properties using functional connectivity MRI (fcMRI).
Methods: Forty-eight participants with schizophrenia and 48 healthy controls underwent resting fMRI scans and clinical evaluations. Six a priori cortical regions of interests (ROIs) were used to derive the six networks: dorsal default mode network (dDMN), fronto-parietal network (FPN), cingulo-opercular network (CON), primary sensorimotor network (SM1), primary auditory network (A1) and primary visual network (V1). The cortico-thalamic connectivity for each network was calculated for each participant and then compared between groups.
Results: A repeated measures analysis of variance (ANOVA) showed significant group × network interactions ($F(5, 90) = 9.5$, $P < 0.001$), which were driven by a significant increase in FC within the SM1 ($t(94) = 4.1$, $P < 0.001$) and A1 ($t(94) = 4.2$, $P < 0.001$) networks in schizophrenics, as well as a significant decrease within the CON ($t(94) = -2.8$, $P = 0.04$). The cortico-thalamic dysconnection did not correlate with symptom severity, representing a state independent abnormality.
Conclusion: The network analysis indicates that cortico-thalamic dysconnection in schizophrenia involves multiple networks and shows network specific changes. The findings provide support for dysfunctional thalamus-related networks in schizophrenia and further elaborate their network properties.

1. Introduction

Schizophrenia is a devastating illness characterized by both abnormal perceptual experiences and by cognitive impairments. Attempts to explain these diverse symptoms with a single underlying mechanism or structure have focused on the thalamus, which has been suggested to play an important role in sensory relay and also in cognitive monitoring (Sim et al., 2006). Consistent with this hypothesis, early structural magnetic resonance imaging (MRI) studies found smaller thalamic volumes in schizophrenia (Andreasen et al., 1990, 1994). Several post-mortem cell count studies in schizophrenics have also found cell abnormalities in the thalamus, especially in the mediodorsal nucleus (MD) and in the pulvinar (Pakkenberg, 1990; Popken et al., 2000; Byne et al., 2002). Gray matter loss in the thalamus was also demonstrated by the modern method of voxel-based morphometry (VBM) (Glahn et al., 2008; Adriano et al., 2010). Thalamic dysfunction has been found by abnormal resting metabolism (Hazlett et al., 2004) and reduced thalamic fMRI activation during cognitive tasks execution (Andrews et al., 2006; Minzenberg et al., 2009). These studies provided consistent evidences for structural and functional abnormalities of the thalamus in schizophrenia.

The thalamus has widespread connections with the cortex and these connections serve not only as a key link in the relay of sensory information from the periphery to the cortex but also in relaying information between cortical areas (Sherman, 2007). Recent developments in resting-state functional connectivity MRI (fcMRI) (Biswal et al., 1995; Greicius et al., 2003) provided an important tool to probe the network dysfunction in schizophrenia and showed preliminary evidences for aberrant cortico-thalamic connections in patients with schizophrenia. Reduced FC between the thalamus and prefrontal cortex in schizophrenics has been found in several fcMRI studies (Zhou et al., 2007; Welsh et al., 2010). One study examined the FC between several regions of interests (ROIs) across the brain and found that FC between the thalamus and post-central gyrus was increased in schizophrenics (Skudlarski et al., 2010). Another fcMRI study, with a seed region in left Wernicke's area,

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explored the relationship between FC and auditory hallucinations. They found that FC between the thalamus and Wernicke's area was increased in the patient group (Hoffman et al., 2011). Because both increased FC and decreased FC have been reported in these studies, cortico-thalamic connections in schizophrenia may crucially depend upon the specific networks involved.

The present study aims to systematically investigate the cortico-thalamic FC within six intrinsic functional networks (ICNs). The first three networks are dorsal default mode network (dDMN) (Raichle et al., 2001; Greicius et al., 2003), cingulo-opercular network (CON) (Dosenbach et al., 2007) and fronto-parietal network (FPN) (Dosenbach et al., 2007; Vincent et al., 2008). These networks were newly defined by fcMRI and received special interest in schizophrenia because of their important roles in the functions of self-related processing, salience attribution and executive controls. The others include three sensorimotor networks: the primary sensorimotor network (SM1), the primary auditory network (A1) and the primary visual network (V1) given the importance of perceptual symptoms in schizophrenia. We used six a priori cortical ROIs in a previous fcMRI study (Shirer et al., 2012), which derived whole set cortical ROIs for different intrinsic networks that nearly cover the whole cortical surface by group independent component analysis (gICA), to derive the thalamic representations of these six networks. The cortico-thalamic FC was calculated for each participant and compared between groups.

2. Materials and methods

2.1. Participants

The schizophrenic group was composed of forty-eight 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 their diagnoses. The patients were also evaluated using the Mini International Neuropsychiatric Inventory Plus (M.I.N.I., (Sheehan et al., 1998). The participants were screened to exclude those with the following conditions: 1) substance abuse or dependence issues over the preceding six months; 2) a history of head injuries that resulted in sustained loss of consciousness, cognitive sequelae, or both; and 3) neurological illnesses or any other disorder that affects cerebral metabolism. With the exception of one non-medicated individual, all the patients used a variety of atypical antipsychotics prior to their participation in the experiment. Forty-eight age-, gender-, and handedness-matched healthy controls were recruited via advertisements. An experienced psychiatrist used the MINI to screen and exclude the candidates with major psychiatric illnesses. In addition, the candidates with histories of Axis-I disorders, including schizophrenia, major depression and bipolar disorder, in their first-degree relatives were excluded. The clinical status of the schizophrenia patients was characterized using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

2.2. Magnetic resonance imaging

The images were acquired using a 3.0 Tesla GE Discovery 750 whole-body high-speed imaging device. Head stabilization was achieved with cushioning, and all the participants wore earplugs (29 dB rating) to attenuate the noise. Automated shimming procedures were performed, and scout images were obtained. The resting-state functional images were collected using a gradient echo T2* weighted sequence (TR/TE/flip = 2500 ms/30 ms/90°). Forty-seven contiguous horizontal slices parallel to the inter-commissural plane (voxel size: 3.5 × 3.5 × 3.5 mm) were acquired and interleaved. These slices covered the cerebellum of each participant. During the functional scans, the participants were instructed to remain awake with their eyes open (each scan lasted 8 min and 24 s across 200 time points). In addition, a high-resolution structural image was acquired in the sagittal plane using a high-resolution sequence (repetition time [TR] = 2530 ms, echo spacing = 7.25 ms, echo time [TE] = 3 ms, flip angle = 7°) and an isotropic 1 mm voxel (FOV 256 × 256).

2.3. Analysis of resting-state functional connectivity

2.3.1. Functional connectivity pre-processing

The motion-corrected functional scans received slice-timing correction and motion correction and were registered to the Montreal Neurological Institute (MNI152) atlas using FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl). Additional preprocessing steps, described in previous reports (Vincent et al., 2008), were used to prepare the data for functional connectivity analysis: 1) spatial smoothing using a Gaussian kernel (6 mm full width at half-maximum), 2) temporal filtering (0.009 Hz < f < 0.08 Hz), and 3) removal of spurious or nonspecific sources of variance by regression of the following variables: (a) the six

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 = 48)	Healthy controls (n = 48)	t	P
Age (years)	34.4 ± 8.2	34.8 ± 8.4	−0.2	.77
Sex	25M/23F	25M/23F	$\chi2 = 0$	1
Education level	14.0 ± 2.0	14.8 ± 1.6	−2.1	.03*
Handedness	48R/0L	46R/2L	$\chi2 = 2.0$	.15
Age at onset	23.3 ± 6.5			
Length of illness (years)	11.7 ± 8.8			
PANSS total	59.5 ± 13.1			
Positive subscale	14.7 ± 4.5			
Negative subscale	15.3 ± 4.4			
General psychopathology subscale	29.5 ± 6.8			
Antipsychotics (chloropromazine equivalent)				
Paliperidone ER (N = 21)	221 ± 71			
Aripiprazole (N = 6)	190 ± 73			
Olanzapine (N = 6)	400 ± 109			
Clozaril (N = 4)	675 ± 377			
Amisulpride (N = 2)	400,200			
Sulpiride (N = 2)	600,100			
Risperidone (N = 1)	200			
Geodon (N = 1)	133			
Haldol (N = 1)	250			
Combination (N = 3)	811 ± 382			

SZ = schizophrenia; M = male; F = female; R = right handed; L = left handed; PANSS = Positive and Negative Syndrome Scale for schizophrenia.
* p<.05

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