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Disrupted thalamo-cortical connectivity in schizophrenia: A morphometric correlation analysis

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ABSTRACT

Increasing studies have implicated the thalamus in schizophrenia, supporting the view that this structure has an important role in this disorder. Given that extensive reciprocal connections exist between the thalamus and the cerebral cortex, it is believed that disruptions of the thalamo-cortical connections may underlie the multiplicity of schizophrenic symptoms. Therefore, assessing the relationship between the thalamus and the neocortex may provide new insights into the pathophysiology of schizophrenia. We analyzed magnetic resonance images from a sample of 101 schizophrenic patients and 101 healthy controls. By assessing the correlation between the thalamic volume and cortical thickness at each vertex on the cortical surface, a thalamo-cortical network was obtained for each group. We compared the patterns of thalamo-cortical connectivity between the two groups. Compared with healthy controls, less distributed cortical regions were identified in the thalamo-cortical network in patients with schizophrenia. Vertex-wise comparison revealed decreased thalamo-cortical connectivity in bilateral inferior frontal gyrus, the left superior temporal gyrus and the right parieto-occipital region in schizophrenia. The observed disruptions in thalamo-cortical connectivity might be the substrate underlying the wide range of schizophrenic symptoms and provide further evidence to support the notion of schizophrenia as a disorder of brain dysconnectivity.

1. Introduction

Schizophrenia is a debilitating mental disorder, which affects close to 1% of the general population. The most profound clinical symptoms of this disease include auditory hallucinations, disordered thinking, delusions, avolition, anhedonia, blunted affect, and apathy (Andreasen, 1997). Cognitive disturbances exist across multiple domains and further affect attention, memory, emotion, motivation, thought and language processes, social functioning, and mood regulation (Hirayasu, 2007). Although extensive studies have been conducted to investigate the pathology of this disease, the pathophysiologic basis underlying this disorder is still not fully understood. Increasing evidences from postmortem, structural and functional imaging studies have implicated the thalamus in schizophrenia, supporting the view that this structure plays an important role in the pathogenesis of schizophrenia (Andreasen et al., 1994; Andreasen, 1997; Andreasen et al., 1998; Portas et al., 1998; Konick and Friedman, 2001). The thalamus is a major conduit for the bidirectional flow of neuronal signals between cortical and subcortical regions and links different cortical regions via transthalamic pathways (Byne et al., 2008). Disruptions of thalamo-cortical circuitry have been postulated to underlie the fundamental schizophrenic symptoms (Andreasen, 1997; Andreasen et al., 1998; Lang et al., 2006). Therefore, assessing the relationship between the thalamus and the neocortex may provide new insight into the pathophysiology of schizophrenia.

Recently, advanced image processing approaches have been developed to measure cortical thickness by calculating the distance between the gray matter and white matter surfaces across the entire cortical mantle. Indeed, cortical thickness is a more direct and biologically meaningful measurement, which is sensitive to neurodevelopmental

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and pathological changes and could reflect the size, density and arrangement of cells (Sowell et al., 2004; Jiang et al., 2009). Morphometric correlational analysis using cortical thickness measurement has been adopted to investigate the structural connectivity pattern between various cerebral regions (Bullmore et al., 1998; McAlonan et al., 2005; Bernhardt et al., 2008). This approach relies on the assumption that significant positive correlations indicate connectivity (McAlonan et al., 2005; Bernhardt et al., 2008, 2009). Correlational study using cortical thickness measurement showed a pattern similar to diffusion tensor imaging data (Lerch et al., 2006; Bernhardt et al., 2008, 2009). By assessing the correlation between the thalamic volume and cortical thickness, we can obtain a whole brain mapping of the thalamo-cortical connectivity. In a diseased population, such correlation analyses allow the assessment of networks that undergo common pathological processes and the localization of disruptions in the cerebral cortex.

Given that the connectivity patterns between the thalamus and the cortex are thought to reflect the vicissitudes of phylogenetic and ontogenetic development (Bullmore et al., 1998; Portas et al., 1998; Mitelman et al., 2005a; Kim et al., 2007; Qiu et al., 2010), the investigation of the correlation between the cortical regions and the thalamus allows us to verify the hypothesis that schizophrenia is a disorder of brain dysconnectivity. Therefore, in the present study, the thalamo-cortical networks were obtained by correlating the cortical thickness and the thalamic volumes of patients with schizophrenia (n = 101) and healthy controls (n = 101). Further analysis was performed to examine the abnormal pattern of the thalamo-cortical connectivity in patients with schizophrenia, compared with healthy controls. We hypothesized that, compared with healthy controls, patients with schizophrenia would exhibit disrupted thalamo-cortical connectivity involving multiple regions across the entire cerebral cortex.

2. Methods and materials

2.1. Subjects

The study was conducted in a medical center, the Taipei Veterans General Hospital (TPE-VGH), in Taiwan. All the subjects were enrolled to the psychiatric department outpatient clinic and day care unit. One hundred and one patients who met the Diagnostic and Statistical Manual of Mental Disorder, fourth edition, or DSM-IV, criteria for schizophrenia, and 101 healthy subjects matched in gender composition and age (healthy control group) were recruited for the study. The healthy control subjects were interviewed using the Mini-International Neuropsychiatric Interview (MINI) to confirm no previous history of neurologic or psychiatric illness, and all had normal brain structure as confirmed by MRI scans. Subjects were excluded if they had any lifetime history of Axis I psychiatric diagnosis, serious neurologic or endocrine disorders, any medical condition or treatment known to affect the brain, alcohol/substance misuse related disorders, or mental retardation defined according to the DSM-IV criteria. The clinical ratings included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for severity of psychopathology. The schizophrenia patients (male/female, 51:50) ranged in age from 17 to 66 (mean age, 36.59; SD, 11.48). The healthy subjects (male/female, 49:52) ranged in age from 19 to 69 (mean age, 36.13; SD, 12.40). For details of the clinical and demographic data for all subjects, see Table 1. All procedures were approved by the institutional review board of the Taipei Veterans General Hospital. Written informed consent was obtained from all subjects.

2.2. Image acquisition

All MR examinations were performed on a 1.5 T MR system (Excite II; GE Medical Systems, Milwaukee, Wis., USA) equipped with an 8-channel head coil in TPE-VGH. To diminish motion artifact generated during the scan, the subject's head was immobilized with cushions inside the coil after the alignment. One hundred twenty-four contiguous axial T1-weighted images (slice thickness = 1.5 mm) were acquired parallel to the anterior–posterior commissure (AC–PC) through the whole head by applying a three-dimensional fluid-attenuated inversion-recovery fast spoiled-gradient recalled echo (FLAIRFSPGR) acquisition sequence (TR = 8.548 ms, TE = 1.836 ms, TI = 400 ms, flip angle = 15°, field of view = 26 × 26 cm, matrix size = 256 × 256).

Table 1
Demographics and clinical data.

	Schizophrenia (n = 101)	Healthy control (n = 101)
Demographics		
Age (years)	36.59 ± 11.48	36.13 ± 12.40
Gender (male/female)	51/50	49/52
Handedness (right/left)	99/2	98/3
Age of onset (years)	26.63 ± 9.26	
Duration of illness (years)	9.99 ± 8.69	
PANSS scores		
Total scores	58.97 ± 16.34	
Positive scores	13.31 ± 4.91	
Negative scores	13.92 ± 4.41	

2.3. Preprocessing

Each scan was processed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) with its volume and surface pipeline (Dale et al., 1999; Fischl et al., 1999a). Starting from the segmentation of the white matter and tessellation of the gray/white matter boundary, an initial surface was obtained after automated topological correction. This surface was used as the initial shape for the deformable model to reconstruct the pial surface. The surfaces were represented by points and triangles composed of the points. Note that the points at the gray/white matter surface had a one-to-one correspondence with the points at the pial surface. After all the surfaces had been reconstructed, the cortical thickness was computed. The thickness was measured in the native space of each subject and defined at each point on the pial surface (as well as its counterpart on the gray/white matter surface because of the one-to-one correspondence) as the mean of the two shortest distances. One was from the point on the pial surface to the gray/white surface, and the other was from the point on the gray/white matter surface to the pial surface. In order to make vertex-wise comparisons, the establishment of vertex correspondence across subjects in a standard surface-based coordinate system was required. Surface based registration was used to build an average template (Fischl et al., 1999b), based on cortical surfaces from all 202 subjects. All of the individual reconstructed cortical surfaces were aligned to the template. Then the cortical thickness data were resampled for each subject. Finally, a heat kernel of 30 mm width was used to smooth cortical thickness maps to increase signal-to-noise ratio and to improve the ability to detect morphometric variations (Chung et al., 2005). The thalamus volume was obtained from the automated procedure for volumetric measures of the brain structures implemented in FreeSurfer (Fischl et al., 2002).

2.4. Statistical analyses

A general linear model (GLM) was fit with thalamic volume as dependent variable, diagnosis as categorical predictors, and total intracranial volume (ICV) as continuous predictors. F-test was done for main effect of diagnosis.

The thalamo-cortical correlation analysis was performed using SurfStat package (http://www.math.mcgill.ca/keith/surfstat/). First, we correlated the thalamic volume with the cortical thickness at each vertex in each group. Significant correlations were interpreted as connections.