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Reduced paralimbic system gray matter volume in schizophrenia: Correlations with clinical variables, symptomatology and cognitive function

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ABSTRACT

Background: Psychopathy is associated with dysfunction in regions that compose the paralimbic system, such as the orbitofrontal cortex (OFC), insular cortex (IC), temporal pole (TP), parahippocampal gyrus (PHG) and cingulate cortex (CC). However, findings of structural alterations in these regions are inconsistent in schizophrenia, and correlations between paralimbic system measures and symptomatology and cognitive function have not been investigated.

Method: 93 patients with schizophrenia and 99 healthy controls received structural magnetic resonance imaging and clinical and cognitive assessment. We compared gray matter volume (GMV) between the two groups using voxel-based morphometry, and evaluated correlations between abnormal GMVs and clinical variables, symptomatology and cognitive function. The assessment of cognition included measures of processing speed, verbal fluency and memory.

Results: Patients with schizophrenia demonstrated significant GMV decreases in the paralimbic system, including bilateral OFC, IC and TP ($p < 0.05$, FWE corrected). GMV decreases were also observed in bilateral superior temporal gyri (STG). The GMVs in bilateral OFC, left IC, left TP and bilateral STG were positively correlated with processing speed, and the GMVs in bilateral OFC were positively correlated with memory function in all participants. In our patient group, the GMV deficits were also associated with earlier age of onset, longer duration of illness, greater number of hospitalizations and more severe positive symptoms.

Conclusions: GMVs in the paralimbic system were significantly reduced in schizophrenia, and these abnormalities were correlated with clinical variables, symptomatology and cognitive function. These results suggest the paralimbic system plays an important role in the pathophysiology of schizophrenia.

1. Introduction

Schizophrenia is one of the most serious and disabling psychiatric disorders, affecting 1% of the population and remaining one of the top ten causes of health burden in the world (Salomon et al., 2012). Schizophrenia is characterized by positive symptoms, negative symptoms and cognitive impairments (Mueser and McGurk, 2004; Fatouros-Bergman et al., 2014). Evidence from

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structural and functional neuroimaging and electrophysiology suggests that the paralimbic system is involved in psychopathology and cognitive impairment (Kiehl, 2006). However, the role of the paralimbic system in the occurrence of schizophrenia is not clear.

The paralimbic system includes the orbitofrontal cortex (OFC), insular cortex (IC), temporal pole (TP), parahippocampal gyrus (PHG) and cingulate cortex (CC). These regions develop in concert in the embryonic period and share cytoarchitecture and connectivity (Mesulam, 1998, 2000). The paralimbic system is a transition zone from agranular to granular cortex (Mesulam, 1998). Enormous inter-individual variability in paralimbic sulcogyral morphology reflects neurodevelopmental processes, including neuronal migration, local neuronal connection, synaptic development, lamination and formation of cytoarchitecture (Rakic, 1988; Armstrong et al., 1995). Meanwhile, the paralimbic system is also a gradually transitive cytoarchitectonic zone between the primitive allocortex of limbic structure and primary sensory-motor areas, which acts as neural bridges that link the inside to the external environment. With information provided by the external environment, the internal milieu is responsible for regulation of emotion, motivation, memory and autonomic-endocrine function (Mesulam, 1998). The paralimbic system plays an important role in the process of mediating internal and environmental targets. Thus, the paralimbic system is engaged in various functions, such as mood regulation, social behavior, attentional and mnemonic processes, reward processing, motivation, and decision-making (Olson et al., 2007; Nakamura et al., 2008; Larquet et al., 2010; Keller et al., 2013; van Eijndhoven et al., 2013), and therefore has been thought to play an important role in the pathophysiology of psychopathy (Kiehl, 2006).

However, studies focused on paralimbic regions in schizophrenia are relatively few, and the published research findings were inconsistent. Structural neuroimaging studies of schizophrenia with small sample sizes have reported reduced gray matter volume (GMV) in one or more paralimbic regions, including GMV in OFC decreases in 24 patients with schizophrenia (Nakamura et al., 2008), GMV in TP decreases in 27 first-episode patients with schizophrenia (Kasai et al., 2003), and GMV in IC decreases in 20 patients with schizophrenia (Saze et al., 2007). However, Lacerda et al. (2007) reported that OFC volume was increased in 43 first-episode schizophrenic patients and correlated with negative symptoms. Similarly, Hoptman et al. (2005) found that GMV of left OFC was increased in 49 chronic schizophrenia or schizoaffective disorder patients, and the OFC volume increase was associated with greater levels of aggression. Additionally, several studies reported that patients with schizophrenia did not significantly differ from controls in TP morphometric variables, and clinical variables were not significantly related to the GMV of TP (Crespo-Facorro et al., 2004; Roiz-Santiáñez et al., 2010). Taken together, these studies suggested that paralimbic regional abnormalities might exist in patients with schizophrenia. However, further investigation is necessary to resolve the inconsistency between studies. In addition, correlations between alterations in the paralimbic system and symptom severity and cognition have not been investigated.

In the present study, we used high-resolution structural magnetic resonance imaging (sMRI) and voxel-based morphometry (VBM) to study abnormalities of GMV in schizophrenia patients, and evaluated correlations between abnormal GMVs and clinical variables, symptomatology and cognitive function. We hypothesized that GMV decreases would be present in the paralimbic system in patients with schizophrenia, and that these alterations would be associated with clinical variables, psychopathology and cognitive deficits.

2. Material and methods

2.1. Participants

This study was approved by the Medical Research Ethics Committee of the Institute of Mental Health, Peking University. All participants provided written informed consent after description of the study. One hundred and nine patients with schizophrenia were recruited from the Institute of Mental Health, Peking University. All patients were assessed by trained psychiatrists using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I, patient edition). Patients with neurologic disorder, a history of serious medical illnesses, substance dependence, pregnancy, or those treated with electroconvulsive therapy within the last 6 months and diagnosis of any other Axis I disorder were excluded. There were 15 patients who were diagnosed with schizophreniform disorder, and all of them received a re-interview at a minimum of 6 months after initial enrollment. They were all finally confirmed with a diagnosis of schizophrenia. All patients were receiving antipsychotic monotherapy, and were not taking antidepressants or mood stabilizers. Medication dosage was converted to chlorpromazine equivalents (Woods, 2003) (see Table 1). Only 4 cases were treated with typical antipsychotics, and all others received atypical antipsychotics. One hundred healthy controls (HCs) were recruited from the local community through advertisements and screened using the SCID-I (non-patient edition). HCs had no life time history of psychotic illness and no family history of psychosis, particularly in first degree relatives. HCs had similar exclusion criteria to patients and were well matched for age, gender and educational level to the patient group (see Table 1 for details). All participants were right-handed.

2.2. Assessment of symptomatology and cognitive function

Symptom severity of all patients was assessed by trained and experienced psychiatrists using the Positive and Negative

Table 1
Clinical variables, symptomatology and cognitive function of schizophrenic patients and healthy controls.

Characteristic	Schizophrenic patients (n = 93)	Healthy controls (n = 99)	Test statistic	*p* Value
Age at scan, years	27.0 (6.6)	25.8 (5.4)	$t = 1.368$	0.173
Gender, male/female, no.	57/36	53/46	$\chi^2 = 1.179$	0.278
Educational level, years	13.7 (2.9)	13.6 (3.4)	$t = 0.230$	0.818
Age of disease onset, years	22.9(6.0)	n.a.		
Illness duration, months	54.1(55.1)	n.a.		
First/relapse, no.	45/48	n.a.		
Paranoid/others, no.	83/10	n.a.		
Times of hospitalization	1.7 (1.4)	n.a.		
PANSS sum score	77.3 (9.5)	n.a.		
PANSS positive score	23.4 (4.2)	n.a.		
PANSS negative score	18.3 (5.8)	n.a.		
PANSS general score	35.7 (5.2)	n.a.		
CPZ-eq at scan(mg/d)	439.1 (205.3)	n.a.		
DSST score	51.9 (13.1)	67.3 (14.0)	$t = -7.685$	<0.001
CFT score	18.7 (5.4)	21.5 (6.5)	$t = -3.278$	0.001
WMS-R score[a]	94.0 (21.4)	108.6 (17.4)	$t = -4.698$	<0.001

PANSS, Positive and Negative Syndrome Scale; CPZ-eq, chlorpromazine equivalents; DSST, Digit Symbol Substitution Test; CFT, Category Fluency Test-animal naming; WMS-R, Wechsler Memory Scale-Revised; n.a.: indicates nor applicable.
Data are given as mean (standard deviation), unless otherwise indicated.
[a] information is missing in 21 patients.

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