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Abnormalities of cingulate cortex in antipsychotic-naïve chronic schizophrenia

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ABSTRACT

While several morphometric studies have postulated a critical contribution of the cingulate cortex (CC) to the pathophysiology of schizophrenia based on abnormalities in CC volume, other studies have been inconclusive. Most such studies have focused only on changes in cortical volume, whereas other morphometric parameters such as surface area and cortical thickness could be more relevant and possibly account for these discrepancies. Furthermore, factors such as antipsychotic drug use and treatment duration may also influence cortical morphology. To clarify the association between schizophrenia and CC deficits, we investigated morphometric abnormalities of the CC in antipsychotic drug (AD)-naïve chronic schizophrenia patients by comparing T1-weighted magnetic resonance images (T1WI-MRI) from patients ($n=17$) to healthy controls ($n=17$) using the surface-based morphometry program FreeSurfer. Partial correlations were examined between abnormal morphometric measures and both clinical variables and cognitive performance scores. Compared to healthy controls, drug-naïve schizophrenia patients exhibited significantly lower volumes in both left rostral anterior CC (rACC) and left posterior CC (PCC). These reductions in CC volume resulted from reduced surface area rather than reduced cortical thickness. There was also a significant relationship between left PCC volume and working memory in patients. No significant correlations were observed between CC volume and clinical variables. The results suggest that abnormalities in the CC as manifested by reduced surface area may contribute to cognitive dysfunction in schizophrenia.

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1. Introduction

The cingulate cortex (CC) is part of the limbic system, a group of highly interconnected structures critical for emotion formation, processing, and expression as well as attention and memory (Devinsky et al., 1995; Hadland et al., 2003; Nielsen et al., 2005). The CC can be divided both anatomically and functionally into the anterior CC (ACC) and the posterior

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CC (PCC) (Vogt et al., 1992). Post-mortem studies have reported cytoarchitectural abnormalities in the ACC, such as loss of interneurons (Benes et al., 1991) and reduced neuron size (Bouras et al., 2001; Chana et al., 2003). Moreover, a meta-analysis of 42 studies on brain structural alterations in schizophrenia identified the CC as one of the gray matter regions with extensive deficits (Ellison-Wright and Bullmore, 2010). Magnetic resonance imaging (MRI) studies of schizophrenics have also found smaller volumes in both ACC (Rametti et al., 2010; Takayanagi et al., 2013; Wang et al., 2007) and PCC (Hulshoff et al., 2001; Koo et al., 2008).

Cortical volume is the product of surface area and cortical thickness. Therefore, a reduction in either surface area or thickness will lead to a decrease in cortical volume. It has been proposed that cortical surface area and thickness are determined by distinct genetic processes, and may reflect different changes in cortical cytoarchitecture (Panizzon et al., 2009; Rakic, 1988). Thus, examination of cortical volume alone may not be sufficient to reveal cortical changes relevant to the pathophysiology of schizophrenia. However, few studies have assessed CC volume, surface area, and thickness simultaneously in patients (Calabrese et al., 2008; Takayanagi et al., 2013; Wang et al., 2007).

Numerous studies have supported a role for CC abnormalities in the cognitive dysfunction and emotional disturbances observed in schizophrenia patients. The ACC and PCC have distinct cytoarchitecture and projection patterns and thus have unique functions; the former is involved in processing of emotional stimuli and mood regulation whereas the latter is involved in memory access and visuospatial orientation (Bush et al., 2000; Vogt et al., 1992; Vogt and Laureys, 2005). The ACC can be further subdivided into rostral and caudal areas. It was proposed that the rostral ACC (rACC) is engaged in emotional regulation, while the caudal ACC (cACC) is involved in cognition (Devinsky et al., 1995) as volumetric reduction in cACC positively correlated with problems in executive function (Haznedar et al., 2004; Szeszko et al., 2000). Reduced ACC activation and cortical thinning have also been reported in schizophrenia (Schultz et al., 2012). Left ACC volume was found to be inversely correlated with negative symptoms (Wang et al., 2007). In contrast, the PCC is believed to be involved in episodic, working, and visuospatial memory (Mitelman et al., 2005), and a larger left PCC volume was associated with fewer negative symptoms (Calabrese et al., 2008). Taken together, numerous studies support a contribution of the CC to schizophrenia, with distinct contributions to symptomology by deficits in ACC and PCC function.

While numerous studies shown morphological abnormalities of the CC in schizophrenia patients (Baiano et al., 2007; Leech and Sharp, 2014), there have also been inconsistencies and contradictory findings. Several studies have suggested that antipsychotics could affect CC morphology. A longitudinal study reported an association between antipsychotic use and gray matter volume reduction in schizophrenia (Ho et al., 2011). Specifically, typical antipsychotics may contribute to significant reductions in gray matter volume (Lieberman et al., 2005). A meta-analysis also suggested that antipsychotics may increase basal ganglia volume (Navari and Dazzan, 2009). Therefore, antipsychotic use may be a potential confounder in morphometric studies showing differences in regional cortical volume between schizophrenia patients and controls. Moreover, the majority of such studies included patients currently taking antipsychotic medications. In antipsychotic drug (AD)-naïve first-episode schizophrenia patients, Lui et al. found right ACC volume reduction (Lui et al., 2009). To the contrary, Kopelman et al. reported increased left ACC volume, but no difference in right ACC in chronic patients under long-term AD treatment (Kopelman et al., 2005). Consequently, examining AD-naïve patients has been emphasized to avoid potential confounds on brain structure.

The aim of the present study is to investigate differences in rACC, cACC, and PCC morphology between controls and AD-naïve chronic schizophrenia patients. In this study, cortical volume, surface area, and thickness of rACC, cACC, and PCC were measured in patients and healthy controls by MRI. In addition, the relationships between deficits in CC morphology and cognitive impairments were investigated using a comprehensive cognitive battery. The hypotheses to be test in this study are: (1) is CC morphology altered in AD-naïve schizophrenia patients compared to healthy controls? (2) Are CC abnormalities correlated with cognitive impairments or clinical symptoms?

2. Results

2.1. Demographic and cognitive measurements

No significant differences were found in mean age, sex ratio, years of education, or ICV between schizophrenia patients and healthy controls. However, the patients showed significant impairment in all cognitive domains tested compared to healthy controls (Table 1).

2.2. Paracingulate gyrus

There was no difference in the occurrence of the paracingulate gyrus between groups (Table 2).

2.3. Cingulate cortical measurements

Compared to healthy controls, patients showed significant volume reductions in left rACC ($F=6.988$, $df1=1$, $df2=30$; $P=0.013$) and left PCC ($F=11.147$, $df1=1$, $df2=30$; $P=0.002$). The surface areas of left rACC ($F=6.036$, $df1=1$, $df2=30$; $P=0.02$) and left PCC ($F=6.343$, $df1=1$, $df2=30$; $P=0.017$) were

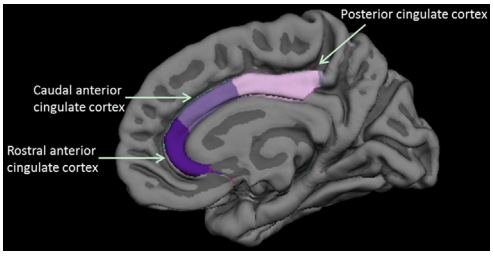

Fig. 1 – Midsagittal views of the rostral anterior cingulate cortex (rACC), caudal anterior cingulate cortex (cACC) and posterior cingulate cortex (PCC).