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Altered asymmetry of the anterior cingulate cortex in subjects at genetic high for psychosis

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ABSTRACT

Objective: Many studies have reported that patients with schizophrenia often have structural abnormalities of the anterior cingulate cortex (ACC) and that some of these seem to be of genetic origin, therefore predating the onset of illness. The present study aimed to investigate whether these alterations in the ACC are genetic in origin by comparing the morphological patterns of three groups: normal controls, subjects at genetic high risk (GHR) for psychosis, and patients with schizophrenia. The relationships between morphological variations and executive function were also investigated.

Methods: This study examined the magnetic resonance images of cingulate sulcus/paracingulate sulcus (CS/PCS) folding patterns in 222 subjects (103 normal subjects, 30 individuals at GHR, and 89 patients with schizophrenia) and evaluated differences in the morphological and asymmetrical patterns of the ACC among groups. Neurocognitive tests were then performed and differences in cognitive performance were analyzed according to morphological variation.

Results: Differences in PCS folding were detected; the control group was significantly more likely than were other groups to show a well-developed left PCS ($p = 0.009$) and leftward asymmetry of the PCS ($p < 0.001$). However, neither GHR subjects ($p = 0.346$) nor patients ($p = 0.784$) showed this leftward asymmetry. No statistically significant differences in CS continuity were observed. A more prominent left PCS ($p = 0.031$) and leftward PCS asymmetry ($p = 0.030$) were both associated with higher scores on the working memory task.

Conclusion: The results suggest that GHR subjects have distinct neurodevelopmental anomalies that resemble those of patients with schizophrenia even though they do not display any psychotic symptoms. Certain developmental alterations in the ACC, such as the loss of leftward sulcal asymmetry in patients with schizophrenia, might be related to genetic factors. Additionally, this morphological alteration might partly account for the impaired executive function in schizophrenia.

1. Introduction

Emerging evidence from genetics, neuroimaging, and neuropathology has reinforced the link between abnormal neurodevelopment and the presentation of schizophrenia (Keshavan, 1999; Pantelis et al., 2005; Fatemi and Folsom, 2009). According to the neurodevelopmental hypothesis, the etiopathological processes of schizophrenia, which involve both genetic and environmental factors, start before the maturation of the brain (Rapoport et al., 2005). One approach to the in vivo study of neurodevelopmental abnormalities involves examining cortical folding patterns. These are formed primarily during the second and third trimesters of gestation and remain relatively constant thereafter. Sulcal/gyral patterns and resulting asymmetries respond robustly to factors that can confound analyses of volumetric imaging methods (Magnotta et al., 1999).

The anterior cingulate cortex (ACC) is involved in brain executive functions such as emotion, motor behaviors, memory or learning (Vogt et al., 1992). Recent neuroimaging research has identified structural abnormalities in the ACC that are correlated with the neuropathology (Fornito et al., 2009) and cognitive deficits observed in schizophrenia (Szeszko et al., 2000; G.M. Clark et al., 2010). A similar study using functional magnetic resonance imaging (fMRI) also revealed that activation patterns in the ACC differed according to sulcal/gyral patterns (Artiges et al., 2006). These findings have a parallel in a previous post-mortem study (Ide et al., 1999) and support the notion that anatomical abnormalities are related to ACC dysfunction in schizophrenia. The paracingulate sulcus (PCS), which belongs to the ACC region, is more commonly found in the left cerebral hemisphere and also seems to be more extensive in the left than the right hemisphere (Paus et al., 1996). Consequently, it

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was reported that healthy subjects tended to have leftward ACC asymmetry (Yücel et al., 2001). Contrastingly, the patients with schizophrenia were apt to have lacked leftward asymmetry (Yücel et al., 2002). It has been proposed that leftward asymmetry in the paracingulate cortex evolved with left hemispheric dominance for language in humans (Paus et al., 1996). The results of imaging studies showing PCS involvement in verbal ability (Fu et al., 2002; G.M. Clark et al., 2010) which might be perceived as a component of executive control (Fornito et al., 2006) support this proposal. Given that cerebral anatomical asymmetries associated with neurodevelopmental processes appear during gestation (Chi et al., 1977), the asymmetries that are characteristic of schizophrenia may reflect a disruption in early neurodevelopment. This is in line with postulates that the genetic mechanism involved in the neurodevelopmental variation of cerebral asymmetry is related to the specific language function of humans and that schizophrenia originates as a "disorder of language disturbance" (Crow, 2008; G.M. Clark et al., 2010). However, structural studies investigating neuroanatomical changes in the ACC have produced inconsistent results due to confounders such as sex and handedness, poorly defined boundaries, and diverse methodologies (Goldstein et al., 1999; Yücel et al., 2001; Fornito et al., 2008a).

Schizophrenia can be considered a highly heritable disease as well as a neurodevelopmental disease (Sullivan et al., 2003). Studies with subjects at genetic high risk (GHR) for psychosis (i.e., nonpsychotic relatives who share genetic factors with patients) can provide useful information about the etiology of schizophrenia while avoiding such confounders as symptoms and treatment effects. Findings reported in the last few years have indicated that certain structural and functional aspects of the brains of GHR subjects differ from those of normal subjects (Keshavan et al., 2005; Gogtay et al., 2007; Jang et al., 2011). Moreover, GHR populations often exhibit abnormalities (Johnstone et al., 2002; Snitz et al., 2006) similar to those in patients with schizophrenia (Allen et al., 2009). Although a few studies have examined the cortical folding patterns of the ACC in individuals with genetic loading for psychosis, most have focused on patients or subjects at ultra-high risk (UHR) (Yücel et al., 2003; Wood et al., 2005). One study found that the left cingulate sulcus (CS) was interrupted and the right PCS was less prominent in male subjects at GHR (Meredith et al., 2012). However, further analysis of relatively homogenous GHR subjects who had remained healthy compared with normal controls was not included.

The degree to which genetic factors are associated with the alterations in ACC morphology observed in schizophrenia regardless of symptoms has not yet been clarified. Additionally, whether anatomical changes in the PCS/CS reflect genetic vulnerabilities and/or the neurodevelopmental etiology of schizophrenia has not yet been established. In this study, we assessed variations in sulcal/gyral morphology and asymmetry patterns to determine whether subjects at greater genetic risk for psychosis show morphological alterations that imply early neurodevelopmental abnormalities in the ACC. We also explored relationships between the morphological pattern in the ACC and performance on cognitive tasks related to executive control including verbal fluency, to investigate functional associations with this variation.

2. Methods

2.1. Participants

Initially, 224 of the 241 individuals meeting the inclusion criteria underwent scans and two (1 with schizophrenia and 1 of the GHR group) were excluded after scanning due to mental retardation and missing information. Ninety patients with schizophrenia were included from the Seoul National University Hospital (SNUH). These patients fulfilled the DSM-IV criteria for schizophrenia according to the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 1996). A total of 103 healthy volunteers were recruited from the community through advertisements. Thirty-one subjects at GHR from the Seoul Youth Clinic were examined; members of this group had two or more relatives with schizophrenia, including one first-degree relative or an identical twin and at least one family member who was at least a fourth-degree relative. Subsets of individuals in the present study constitute an extension of the sample in our previous studies, as per protocols described in previous publications (Jang et al., 2011; Byun et al., 2012). Handedness was assessed using Annett's questionnaire (Annett, 1976). Exclusion criteria for all groups were as follows: history of significant head injury, neurological disease, significant medical illness, intelligence quotient (IQ) less than 70, and substance use disorder. All patients were taking antipsychotics at the time of scanning. The severity of symptoms in patients was evaluated with the Positive and Negative Symptom Scales (PANSS) (Kay et al., 1987). GHR subjects were assessed using the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2002; Jung et al., 2010), the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2002), and the PANSS. IQ was evaluated using the Korean version of the Wechsler Adult Intelligence Scale (K-WAIS) (Kim and Lee, 1995).

This study was approved by the Institutional Review Board at SNUH, and written informed consent was obtained from all participants after the procedures had been explained.

2.2. Magnetic resonance imaging (MRI)

All MRI scans were acquired on an axial plane using a 1.5-T scanner and a T1-weighted 3-D magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence. We loaded all scans into Analyze (Version 8.1, Mayo Clinic) and spatially realigned them along the anteroposterior axis parallel to the intercommissural line. We conducted scans at two different sites. Parameters for the scans were as follows: at SNUH, 1.5-T Signa Scanner (General Electric): echo time/repetition time = 5.5/14.4 ms, flip angle = 20°, field of view = 210 mm, slice thickness = 1.5 mm, voxel dimensions = $0.82 \times 0.82 \times 0.82$ mm^3; at National Medical Center, 1.5-T Avanto scanner (Siemens): echo time/repetition time 4.76/1160 ms, flip angle = 15°, field of view = 230 mm, slice thickness = 0.9 mm, voxel dimensions = $0.45 \times 0.45 \times 0.90$ mm^3. The intracranial volume (ICV) was estimated by aggregating all volumes including the gray matter, white matter and cerebrospinal fluid.

2.3. Classification of ACC morphology

Analysis was done on a sagittal plane and in a region with several boundaries. The aligned anterior commissure–posterior commissure (AC–PC) line was set as a horizontal boundary, and the vertical anterior commissure (VAC) was set as a vertical boundary. The slice with the most distinguished CS and PCS was chosen within ten parasagittal slices for each hemisphere. One rater (H.Y.P.) who was blind to the group of each subject determined the continuity of the CS and PCS and measured the length of the PCS. We randomly selected 20 cases for reliability assessment, and these cases were re-rated by two individual raters (H.Y.P. and J.Y.H.). Intra- and inter-rater reliabilities were $k = 0.92$ and $k = 0.80$, with disagreement weighted as 6 for the PCS and 1.0 for the CS.

2.3.1. Paracingulate morphology and cingulate continuity

The CS was classified as "continuous" or "interrupted" following the methods described by Paus et al. (1996). It was considered continuous in the absence of a clear interruption of at least 10 mm in length. If more than one interruption in the CS was observed, the longest interruption was measured.

We classified the PCS in each hemisphere into one of three groups according to sulcal maturation using the protocol suggested by Yücel et al. (2001) and applied in previous research (Yücel et al., 2002, 2003; Wood et al., 2005; Artiges et al., 2006; Shim et al., 2009): "prominent," "present," and "absent" (Fig. 1). If the PCS exceeded 40 mm