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Increased Occipital Gyrification and Development of Psychotic Disorders in Individuals With an At-Risk Mental State: A Multicenter Study

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ABSTRACT

BACKGROUND: Anomalies of brain gyrification have been reported in schizophrenia, possibly reflecting its neurodevelopmental pathology. However, it remains elusive whether individuals at risk for psychotic disorders exhibit deviated gyrification patterns, and whether such findings, if present, are predictive of transition to psychotic disorders.

METHODS: This multicenter magnetic resonance imaging study investigated brain gyrification and its relationship to later transition to psychotic disorders in a large sample of at-risk mental state (ARMS) individuals. T1-weighted magnetic resonance imaging scans were obtained from 104 ARMS individuals, of whom 21 (20.2%) exhibited the transition to psychotic disorders during clinical follow-up (mean = 4.9 years, SD = 2.6 years), and 104 healthy control subjects at 4 different sites. The local gyrification index (LGI) of the entire cortex was compared across the groups using FreeSurfer software.

RESULTS: Compared with the control subjects, ARMS individuals showed a significantly higher LGI in widespread cortical areas, including the bilateral frontal, temporal, parietal, and occipital regions, which was partly associated with prodromal symptomatology. ARMS individuals who exhibited the transition to psychotic disorders showed a significantly higher LGI in the left occipital region compared with individuals without transition.

CONCLUSIONS: These findings suggested that increased LGI in diverse cortical regions might represent vulnerability to psychopathology, while increased LGI in the left occipital cortex might be related to subsequent manifestation of florid psychotic disorders as a possible surrogate marker.

Keywords: At-risk mental state, Local gyrification index, Magnetic resonance imaging, Multicenter, Occipital cortex, Psychotic disorders

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Psychotic disorders have disabling features, including functional impairments (1) and premature mortality (2,3); however, early intervention trials to delay or prevent the onset of full-blown psychotic disorders among high-risk individuals have shown limited success (4). To overcome the high false positive rate (5) in clinical high-risk cohorts (i.e., at-risk mental state [ARMS]) for effective early intervention, it is crucial to identify surrogate biological markers of the development of overt psychotic symptoms using a large ARMS cohort with and without later transition to psychotic disorders.

Magnetic resonance imaging (MRI) studies in individuals with ARMS have reported several brain structural changes before the onset of psychotic disorders; ARMS subjects who subsequently exhibit the transition to psychotic disorders (ARMS-T) have prominent gray matter reduction in frontal and temporolimbic regions (6–9), while several studies reported no significant relationship between the onset of psychotic disorders and gray matter reduction (10,11), or an even larger volume of the hippocampus in ARMS-T subjects (12). These discrepancies could be partly attributable to longitudinal gray matter changes with age (13), disease process (14), and/or medication effects (15).

Brain gyrification is a potential marker of early neurodevelopment, as gyral and sulcal formation takes place between 10 and 15 weeks of gestation and mostly finishes by the third trimester of fetal life (16). In previous MRI studies that examined the gyrification index (GI), although not consistently replicated (17), first-episode schizophrenia patients likely indicate widespread cortical hypergyria (18–22), which is reported to be associated with executive dysfunction

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as well as symptom severity (22). The mechanisms of gyral anomalies in schizophrenia remain elusive, but they may reflect regional disruption of axonal connectivity during early development (23,24). Although there are still a limited number of gyrification studies in high-risk subjects for psychotic disorders, preliminary evidence from 2-dimensional measurement of GI suggests that genetic (25) and clinical (21) high-risk subjects have increased gyrification of frontal/parietal regions, and that frontal hypergyrification in genetic high-risk subjects is also associated with later development of overt psychotic disorders (26). Other indexes of gross surface morphology, such as the sulcogyral pattern, sulcal count, and/or sulcal depth in the orbitofrontal cortex, may be predictive of future transition to psychotic disorders (27,28). However, these previous studies, investigating two-dimensional GI from selected frontal and parietal slices or surface morphology in selected frontal regions, cannot address the regional specificity of brain gyrification findings in high-risk cohorts.

In this study, we conducted a multicenter investigation to obtain a large sample size of subjects with ARMS for sufficient statistical power. We recruited ARMS individuals and matched healthy comparison subjects at 4 scanning sites in Japan. We aimed to investigate the gyrification of the entire cortex in the study participants using the local GI (LGI), which has methodological advantages over other methods by taking into account the inherent 3-dimensional nature of the cortical surface (29). On the basis of previous high-risk studies, we predicted that ARMS subjects, especially those who later developed psychotic disorders, would have a hypergyrification pattern as compared with healthy control subjects.

METHODS AND MATERIALS

Participants

One hundred four individuals with ARMS were recruited from domestic specialized clinical services for ARMS at Toyama University Hospital, The University of Tokyo Hospital, Toho University Hospital, and Tohoku University Hospital (30,31). Each individual fulfilled the criteria of ARMS according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) (32) (Toyama and Tohoku) or the Structured Interview for Prodromal Symptoms/the Scale of Prodromal Symptoms (SIPS/SOPS) (33) (Tokyo and Toho). The ARMS individuals were prospectively followed regularly at each site (mean = 4.9 years, SD = 2.6 years) and divided into 1) those individuals who subsequently made the transition to psychotic disorders (ARMS-T) (n = 21 [20.2%]), 2) those individuals who did not exhibit the transition to psychotic disorders during clinical follow-up of at least 2 years (ARMS-NT) (n = 69), or 3) those individuals with unknown outcome because of dropout within 2 years (n = 14). Transition to psychotic disorders was determined at each site according to the CAARMS criteria (i.e., at least one fully positive psychotic symptom several times per week for more than 1 week) or the SIPS criteria (i.e., the presence of a positive symptom that has existed for more than 1 month or accompanying a serious disorganization or danger). The diagnoses of psychotic disorders in ARMS-T subjects based on the criteria of the DSM-IV (34) were schizophrenia (n = 14), delusional disorder (n = 1), schizophreniform disorder (n = 1), brief psychotic disorder (n = 1), and psychotic disorder not otherwise specified (n = 4). At the time of MRI scanning, 41 of the 104 ARMS individuals (39.4%) were receiving a low dosage of antipsychotics for their relatively severe symptoms (e.g., rapid deterioration and suicidal risk) according to the International Clinical Practice Guidelines for Early Psychosis (35). Medication dose, duration between scanning and transition, and other clinical data are summarized in Table 1. Gender- and age-matched control individuals consisted of 104 healthy volunteers who were recruited from the community, hospital staff, and university students at each site.

The exclusion criteria for all groups were 1) having a lifetime history of serious head injury, neurological illness, or other serious physical disease; 2) fulfilling the criteria for substance abuse/dependence, including cannabis use; and 3) having previous psychotic episodes that met the DSM-IV criteria. This study was approved by the Committees on Medical Ethics of each site. After a complete explanation of the study was provided, written informed consent was obtained from all individuals.

MRI Data Acquisition

T1-weighted MRI images were obtained at baseline at each site as follows.

University of Toyama. The subjects were scanned using a 1.5T scanner (Magnetom Vision, Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence fast low-angle shot MRI yielding 160 to 180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were the following: repetition time (TR) = 24 ms; echo time (TE) = 5 ms; flip angle = 40°; field of view = 256 mm; and matrix size = 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm.

The University of Tokyo. The subjects were scanned using a 3.0T MRI scanner (Signa; GE Healthcare, Milwaukee, WI), with a three-dimensional Fourier transform fast-spoiled gradient recalled acquisition with steady state yielding 176 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were the following: TR = 6.80 ms; TE = 1.94 ms; flip angle = 20°; field of view = 240 mm; matrix size = 256 × 256 pixels. The voxel size was 0.9375 × 0.9375 × 1.0 mm.

Toho University. The subjects were scanned using a 1.5T scanner (EXCELART Vantage, XGV 1.5 T; Toshiba Medical Systems, Tokyo, Japan), yielding 160 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were the following: TR = 24.4 ms; TE = 5.5 ms; flip angle = 35°; field of view = 250 mm; matrix size = 256 × 256 pixels. The voxel size was 0.98 × 0.98 × 1.0 mm.

Tohoku University. The subjects were scanned using a 1.5T scanner (Achieva, Phillips Medical Systems, Best, the Netherlands) with a three-dimensional fast field echo sequencing yielding 200 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters