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No regional gray matter volume reduction observed in young Japanese people at ultra-high risk for psychosis: A voxel-based morphometry study

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ABSTRACT

Objectives: Structural brain magnetic resonance imaging studies of individuals at ultra-high risk (UHR) for psychosis have shown subtle but widespread reductions in baseline gray matter volume (GMV) in the frontal, temporal, and limbic regions compared with healthy controls (HC). These regions coincide with regions of reduced GMV in patients with established psychosis and have led to the consideration of structural changes in UHR as a potential biomarker for future transition to psychosis. However, most studies have been from Europe, North America, and Australia, with few reports from other regions, and two recent studies from Asian countries have failed to detect regional GMV reduction in UHR, suggesting the need for further analysis of an Asian sample. In this study, we investigated GMV reduction in Japanese UHR subjects. Results: The study used voxel-based morphometry to compare magnetic resonance imaging brain scans between 45 UHR individuals recruited by a specialist and 33 HCs. This showed no significant GMV reduction in the UHR group compared with the healthy control group. This negative result may be attributable to characteristics of Asian samples, such as a low prevalence of illicit drug use, or to the heterogeneous nature of UHR subjects.

1. Introduction

It is important to identify individuals who are at ultra-high risk (UHR) for developing psychosis, i.e., those in a putative prodromal state for psychotic disorders (McGorry et al., 2009). To identify potential biomarkers for this state, there have been extensive structural magnetic resonance imaging (MRI) studies, including investigations of a reduction in baseline regional gray matter volume (GMV) (Jung et al., 2010). Such studies have increased with the development of voxel-based morphometry (VBM), a relatively easy-to-use automated neuroimaging analysis technique (Ashburner and Friston, 2000; Whitwell, 2009).

VBM studies of UHR subjects conducted in Europe, North America, and Australia have shown subtle but widespread baseline reductions in GMV, compared with healthy controls (HCs), in the frontal, temporal, and limbic regions (Fusar-Poli et al., 2011). These regions coincide with regions of GMV reduction observed in patients with first-episode schizophrenia (Ellison-Wright et al., 2008; Steen et al., 2006; Vita et al., 2006) and psychosis (Fusar-Poli et al., 2012b). This has led researchers to consider that such structural changes of UHR could be used as a potential biomarker for predicting a future transition to psychosis (Smieskova et al., 2010).

When establishing a potential biomarker, it is essential to ensure that there is consistency across different populations. However, there have been few studies of GMV reduction in UHR subjects outside Western countries. Furthermore, two recent VBM studies from Asian countries (Klauser et al., 2015; Nakamura et al., 2013) have failed to detect regional GMV reductions in UHR subjects. This suggests the need for further investigation using another Asian sample. In this study,

Abbreviations: ARMS, at-risk mental state; GMV, gray matter volume; HC, healthy controls group; PANSS, Positive and Negative Syndrome Scale; UHR, ultra-high risk group; VBM, voxel-based morphometry

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Table 1
Demographic and clinical characteristics of the participants.

	UHR (N = 45)	HC (N = 33)	Statistics	p value
Age (years)	21.0 ± 5.0	23.5 ± 5.1	t = −2.16	0.034
Male/Female	18/27	11/22	χ^2 = 0.362	0.547
Educational level (years)	12.1 ± 2.3	15.1 ± 1.7	t = −6.19	< 0.001
Intracranial volume (cm^3)	1520 ± 147	1523 ± 149	t = −0.102	0.919
Drug (mg/day, chlorpromazine equivalent)	84 ± 195			
Antipsychotic medication (yes/no)	12/33			
PANSS positive	14.8 ± 3.8			
PANSS negative	13.8 ± 3.7			
Days from first visit to MRI scan	83 ± 116			

Data are presented as number or mean ± standard deviation. Abbreviations: UHR, ultra-high risk group; HC, healthy controls group; PANSS, Positive and Negative Syndrome Scale.

therefore, we used VBM to investigate whether baseline GMV reduction could be detected in Japanese UHR subjects.

2. Methods

2.1. Participants

This study enrolled 45 UHR individuals (the UHR group) and 33 HC groups. Table 1 summarizes the demographic and clinical characteristics of the participants.

The UHR group participants were recruited at the Sendai at-risk mental state and first episode (SAFE) clinic at the Department of Psychiatry at Tohoku University Hospital in Sendai, Japan, a specialist clinic for patients with early psychosis (Katsura et al., 2014; Mizuno et al., 2009). All were assessed by trained and experienced psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Japanese version of the Comprehensive Assessment of At-risk Mental States (Miyakoshi et al., 2009), with the final diagnoses confirmed at a consensus meeting of clinical staff. All participants in the UHR group met one or more of the three UHR criteria (Yung et al., 2003): attenuated positive symptoms (APSs); brief limited intermittent psychotic symptoms (BLIPS); and/or state and trait risk factors with functional decline. Additional inclusion criteria for the UHR group were that the participants were aged 14–35 years, seeking psychiatric help, and were Japanese speaking. The exclusion criteria were as follows: a history of a previous psychotic disorder or manic episodes that fulfilled the diagnostic criteria of bipolar I disorder specified in DSM-IV-TR (American Psychiatric Association, 2000); a serious risk of suicide or violence because of a personality disorder; substance abuse or addiction within one year of inclusion; known intellectual disability (IQ < 70); a history of neurological disorders, head injury, or any other significant medical condition associated with psychiatric symptoms. The participants were asked about the current and past histories of substance use, including cannabis, and if they had a history, then they were assessed to check whether they met the criteria of substance abuse/dependence according to DSM-IV-TR (American Psychiatric Association, 2000).

The HC group participants were recruited from a local university. None met the DSM-IV criteria for any disorders, and none had a history of psychiatric treatment.

The Ethics Committee of the Tohoku University Graduate School of Medicine and the Tohoku University Hospital approved this study. All participants aged over 18 years provided written informed consent. For the participants younger than 18 years their parents provided written informed consent and the participants gave their written assent.

2.2. Characteristics of the UHR group

Of the 45 UHR group participants, 38 (84%) showed APSs only, one (2%) showed BLIPS only, two (4%) showed state and trait risk factors only, three (7%) showed both APSs and state and trait risk factors, and one (2%) showed both APSs and BLIPS. All were evaluated with at least 12 months follow-up after scanning. During follow-up, nine (20%) transitioned to psychosis; the other 36 (80%) did not transition to frank psychosis.

At the time of scanning, 12 of the UHR group participants were being treated with antipsychotics at a mean ± standard deviation chlorpromazine equivalent of 84 ± 195 mg/day. One was treated with a typical antipsychotic, levomepromazine, and 11 were treated with atypical antipsychotics, including aripiprazole (n = 3), quetiapine (n = 3), blonanserin (n = 2), olanzapine (n = 1), perospirone (n = 1), and risperidone (n = 1). None of the participants had current and past histories of illicit substance use, including cannabis.

2.3. MRI acquisition

The MRI scans for the UHR and HC groups were acquired with the same system and by using the same protocol. MRIs were acquired with a 1.5-T system (Achieva, Philips Medical System) using a three-dimensional fast field echo sequence with sensitivity encoding (SENSE), yielding 200 contiguous T1-weighted slices in the sagittal plane with 1.0 mm thickness each. The imaging parameters were as follows: repetition time = 30 ms, echo time = 5 ms, flip angle = 30°, field of view = 256 mm, and matrix size = 256 × 256 pixels. The voxel size was 1.0 mm × 1.0 mm × 1.0 mm.

2.4. MRI data preprocessing

Differences in GMV between the UHR and HC groups were evaluated using VBM analysis (Ashburner and Friston, 2000). This was performed with the diffeomorphic anatomical registration using a exponentiated lie algebra (DARTEL) tool (Ashburner, 2007) in Statistical Parametric Mapping 12 (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm) running under MATLAB 8.0 (The MathWorks, Inc., USA). The DARTEL analysis was chosen to maximize accuracy and sensitivity (Yassa and Stark, 2009).

Each participant's MRIs were visually inspected for scanner artifacts and gross anatomical abnormalities before they were segmented into gray matter (GM), white matter, and cerebrospinal fluid using the standard unified segmentation model in SPM12. Study-specific GM templates were created using DARTEL, and the GM data were spatially normalized and warped in DARTEL and transformed to Montreal Neurological Institute (MNI) space (http://www.mni.mcgill.ca/). The images were then Jacobian scaled to ensure that GM volumes were preserved following the spatial normalization procedure. We used standard smoothing of 8-mm full width at half maximum. This preprocessing provided smooth, modulated, and normalized data that were used for the statistical analysis. The total intracranial volume (ICV) was calculated for each participant by summing the total tissue probabilities for GM, white matter, and cerebrospinal fluid from the probability maps generated during the initial segmentation.

2.5. Statistical analysis

Differences between the groups in demographic characteristics and clinical profiles were examined using t-tests and one-way analysis of variance for parametric data, and a chi-square test for nonparametric data. The statistical analysis was performed using SPSS software (version 17.0 for Windows; SPSS Inc., Chicago, IL). The level of statistical significance was defined as $p < 0.05$ (two-tailed).

Differences in GMV between the groups were analyzed using two-sample t-tests implemented using the general linear model approach