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Regional gray matter reduction correlates with subjective quality of life in schizophrenia

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ABSTRACT

Subjective quality of life (QOL) has been recognized as an important consideration in schizophrenia. Several symptoms and neurocognitive functions were shown to be correlated with subjective QOL; however its determinants are not well understood. In this study, we investigated the association between brain structural abnormalities and subjective QOL in patients with schizophrenia. Forty-five schizophrenia patients and 48 age, sex, and education-matched healthy participants underwent magnetic resonance imaging (MRI), and the Schizophrenia Quality of Life Scale (SQLS) was used to rate subjective QOL. We performed voxel-based morphometry (VBM) to investigate regional brain alterations. Relative to normal controls, schizophrenia patients exhibited gray matter reductions mainly in the frontal and temporal regions. Worse psychosocial subscale of SQLS was associated with gray matter (GM) reduction in the right dorsolateral prefrontal cortex (DLPFC), and worse motivation/energy subscale was associated with gray matter reduction in the left superior frontal sulcus, left parahippocampal gyrus, and the left inferior temporal gyrus. The correlation between DLPFC GM volume and psychosocial subscale of SQLS disappeared after controlling for severity of psychopathology, while the other correlations remained significant when controlled by demographic and clinical variables. Combining imaging techniques with psychosocial methods would help to elucidate those factors that are associated with QOL.

1. Introduction

Quality of life (QOL) is an important consideration for patients with schizophrenia (Hofer et al., 2005). QOL is defined as a person's sense of well-being, life satisfaction and health status (Lehman, 1997). Previous studies have investigated predictors of QOL in schizophrenia, and several studies reported sociodemographic factors, depressive mood, and psychiatric symptoms as important determinants for QOL (Jin et al., 2001; Hofer et al., 2005; Aki et al., 2008; Yamauchi et al., 2008; Narvaez et al., 2008).

Among the psychiatric symptoms, severity of both positive symptoms (Gaite et al., 2002; Ritsner, 2003; Thornicroft et al., 2004) and negative symptoms (Packer et al., 1997; Heslegrave et al., 1997; Aksaray et al., 2002) have been associated with worse QOL. Although, previous studies show some inconsistency, recent meta-analysis found weak but significant correlations between positive and negative symptom levels and QOL (Eack and Newhill, 2007).

Brain magnetic resonance imaging (MRI) studies have demonstrated multiregional gray matter (GM) reductions in patients with schizophrenia (Haijma et al., 2012; Suzuki et al., 2005). Voxel-based morphometry (VBM; Ashburner and Friston, 2000) is an automated imaging-analysis method for exploring regional GM alterations in

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the whole brain. Recent meta-analyses of VBM studies of patients with schizophrenia showed GM reductions in such regions as the medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, superior temporal gyrus (STG), insula, parahippocampal gyrus, amygdala, thalamus, and striatum (Ellison-Wright et al., 2008; Glahn et al., 2008). Some of these regional GM alterations were found to be related to symptom severity in schizophrenia patients. For instance, a large sample VBM study (Koutsouleris et al., 2008) reported associations between the abnormalities in the perisylvian region and positive symptoms, and a meta-analysis (Bora et al., 2011) reported an association between the abnormalities in the medial frontal gyrus/orbitofrontal cortex and negative symptoms.

Thus, the previous studies suggest associations between QOL and symptoms, and between GM and symptoms. Our interest in this study was to explore the more detailed nature of the interrelationship among QOL, symptoms, and GM pathology, using VBM. We expected associations among some aspects of QOL, positive symptoms, and perisylvian GM pathology, and associations among other QOL aspects, negative symptoms, and prefrontal GM pathology.

2. Methods

2.1. Participants

The schizophrenia group comprised 45 patients (25 men and 20 women, 42 right-handed and 3 left-handed) who were referred to the Department of Neuropsychiatry, Kyoto University Hospital. Each patient fulfilled the criteria for schizophrenia based on the Structural Clinical Interview for DSM-IV (SCID). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). All patients were receiving antipsychotic medication (first-generation [$n = 4$], second-generation [$n = 31$], first and second generation [$n = 10$]). The medication dosage on the day of scanning was converted to haloperidol equivalent according to the practice guidelines for the treatment of patients with schizophrenia (Inagaki and Inada, 2008; Lehman et al., 2004). They were all physically healthy at the time of scanning. None had a history of neurological injury or disease, severe medical illness, or substance abuse that may affect brain function. The comparison group comprised 48 healthy individuals (26 men and 22 women, 47 right-handed and 1 left-handed) who were matched to the schizophrenia group with respect to age, gender, and education level. They were also evaluated on the basis of SCID and had no history of neurological or psychiatric disease and no first-degree relatives with psychotic episodes. Vocabulary and block design subtests of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) was used to estimate the verbal IQ (VIQ) and the performance IQ (PIQ) respectively, by transforming the scores corrected for age into *T* scores.

This study was approved by the Committee on Medical Ethics of Kyoto University and carried out in accordance with The Code of Ethics of the World Medical Association. After a complete description of the study to the participants, they provided written informed consent.

2.2. The Schizophrenia Quality of Life Scale Japanese version (SQLS)

The Japanese version of the Schizophrenia Quality of Life Scale (SQLS) (Wilkinson et al., 2000; Kaneda et al., 2002) was used to assess subjective QOL of schizophrenia patients. With its good reliability and validity, it has been widely used in previous studies on patients with schizophrenia to assess subjective QOL (Yamauchi, 2008; Ogino et al., 2011). It is a self-report 30-item questionnaire for measuring QOL specific to patients with schizophrenia. It is composed of three subscales: psychosocial, motivation/energy, and symptoms/side-effects. Each of the thirty items is rated on a five-point Likert scale ranging from 0 (strongly disagree) to 4 (strongly agree), and lower scores indicate higher levels of subjective QOL.

2.3. MRI acquisition and pre-processing

All participants underwent MRI scans on a 3-T whole-body scanner with a 40 mT/m gradient and a receiver-only 8-channel phased-array head coil (Trio, Siemens, Erlangen, Germany). The scanning parameters of the three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequence were as follows: TR = 2000 ms, TE = 4.38 ms, TI = 990 ms, FOV = 225 × 240 mm, matrix = 240 × 256, resolution = 0.9375 × 0.9375 × 1.0 mm^3, and 208 total axial sections without intersection gaps. MRI data were processed and analyzed using an extension of statistical parametric mapping 5 (SPM5; Welcome Department of Imaging Neuroscience, London, UK), specifically, the VBM5.1 toolbox written by Gaser (http://dbm.neuro.uni-jena.de/vbm) running in Matlab 2007b (Math Works, Natick, MA, USA). A unified segmentation model (Ashburner and Friston, 2005) was used, which combined both normalization and segmentation parameters in a single generative model. The output images of GM, white matter (WM), and cerebrospinal fluid (CSF) partitions were resliced into 1 × 1 × 1 mm voxels. The voxel values of segmented and normalized GM images were multiplied (modulated) by the Jacobian determinants obtained from non-linear normalization steps. The resultant GM images were smoothed with Gaussian kernels of 12 mm full width at half maximum, on which all analyses were performed.

2.4. Data analyses

2.4.1. Correlation of SQLS score with clinical and demographic measures

Correlational analyses were performed between the SQLS subscale scores and clinical (PANSS scores, duration of illness, and medication level) and demographic (age, gender, and education) variables and IQs. Data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$. Because of the exploratory nature of this analysis, multiple comparison correction was not performed.

2.4.2. Regional GM reductions in patients relative to controls

To identify the brain regions where patients with schizophrenia showed GM reductions relative to controls, a two-sample *t*-test was undertaken in SPM5. The effects of age and gender were excluded from the data as nuisance covariates. A liberal statistical threshold of $p < 0.05$ (uncorrected) with an extent threshold of 100 voxels was applied to create an inclusion mask for following correlational analyses. MNI coordinates were transformed into Talairach coordinates (Talairach and Tournoux, 1988) using the mni2tal.m Matlab script written by Matthew Brett (http://imaging.mrccbu.cam.ac.uk/imaging/MniTalairach).

2.4.3. Correlation of SQLS scores with GM volume

To identify the overall brain regions wherein the schizophrenia patients showed volume changes correlated with the SQLS subscale scores, multiple regression analyses were undertaken in SPM5 for each SQLS subscale, with age and gender as nuisance covariates and above-described group difference region as the inclusion mask. First, the statistical threshold was set at $p < 0.05$ (uncorrected) with an extent threshold of 100 voxels. To depict the overall pattern of relationship between brain structure and QOL, we set this liberal statistical threshold. Second, for representative clusters which were