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Alexithymia and regional gray matter alterations in schizophrenia

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ABSTRACT

Alexithymia is characterized by deficits in emotional self-awareness. Although alexithymia refers to a deficit in recognizing one's own emotions, some studies have focused on the relation between alexithymia and impaired social cognition. An association between alexithymia and schizophrenia has been previously reported, but the brain structures involved remain unclear. The present study investigated associations between alexithymia and specific brain structures to determine whether these regions overlapped with key structures underlying social cognition. Twenty-one patients with schizophrenia and 24 age-, gender- and education level-matched healthy controls underwent structural magnetic resonance imaging. Alexithymia was assessed using the 20-item Toronto Alexithymia Scale (TAS-20). We applied voxel-based morphometry to investigate the correlation between TAS-20 scores and regional brain alterations. TAS-20 scores were significantly higher in patients than controls. Bilateral ventral striatum and left ventral premotor cortex volumes were negatively correlated with TAS-20 total scores in controls, while left supramarginal gyrus (SMG) volume was negatively correlated with TAS-20 total scores in patients. These results suggest that schizophrenia is associated with alexithymia, and that gray matter alterations of the left SMG constitute a key pathology underlying alexithymia in schizophrenia. This association may be related to deficits in self–other distinction, self-disturbance, and language processing in schizophrenia.

1. Introduction

"Alexithymia" is a term derived from the Greek, meaning "lack (*a*)", "word (*lexis*)", and "emotion (*thymos*)", and refers to deficits in recognizing, processing, and verbalizing emotions. The phenomenon was first described in patients with psychosomatic disorders (Sifneos, 1972) and was considered to represent difficulty discriminating between self emotional states and bodily sensations, as well as a shift in communicative styles, which are involved in the application of language (Taylor, 1984). A number of subsequent studies reported that alexithymia is found in other psychiatric disorders including eating disorders (Taylor et al., 1996; Bydlowski et al., 2005; Gilboa-Schechtman et al., 2006), dissociative disorders (Zlotnick et al., 1996; Elzinga et al., 2002; Sayar et al., 2005), posttraumatic stress disorder (Krystal et al., 1986; Alvarez and Shipko, 1991; Frewen et al., 2008), and pervasive developmental disorders (Fitzgerald and Molyneux, 2004; Tani et al., 2004; Szatmari et al., 2008). A relationship between alexithymia and schizophrenia has also been previously reported (Stanghellini and Ricca, 1995; Maggini and Raballo, 2004; Todarello et al., 2005; van't Wout et al., 2007).

Meanwhile, impairments in various domains of social cognition have been highlighted in recent studies of schizophrenia. A number of studies have demonstrated impaired facial emotion processing (Mandal et al., 1998), theory of mind (ToM; Premack and Woodruff, 1978) abilities (Frith and Corcoran, 1996; Brüne, 2005), and empathy (Bora et al., 2008; Derntl et al., 2009) in schizophrenia.

Although alexithymia refers to a deficit in emotional self-awareness, rather than a deficit in the recognition of others' emotions, Guttman and Laporte (2002) reported that alexithymia is inversely related to the ability of empathy. In addition, Dimaggio et al. (2008) noted that a representation of the self may act as a model for understanding the minds of others. That is, to understand what people are thinking about or how they feel, it may be crucial to understand and process our own emotions. As such, we hypothesize that impairments in social cognition and alexithymia may be co-existent and intercorrelated in schizophrenia.

Brain magnetic resonance imaging (MRI) studies have demonstrated multiregional brain alterations in patients with schizophrenia. Disproportionate gray matter (GM) reductions in a variety of

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prefrontal and temporal subregions have often been reported in previous structural MRI studies using manual volumetry (Shenton et al., 2001; Suzuki et al., 2005). Voxel-based morphometry (VBM; Ashburner and Friston, 2000) is a widely used, automated imaging-analysis method for exploring regional GM alterations throughout the whole brain. Recent meta-analyses of VBM studies in patients with schizophrenia have revealed widely consistent findings of GM reductions in bilateral superior temporal gyrus, bilateral medial prefrontal cortices, bilateral inferior frontal gyrus, right anterior cingulate gyrus, bilateral insula, bilateral parahippocampal gyrus, thalamus, and the left uncus/amygdala region (Honea et al., 2005; Ellison-Wright et al., 2008).

Moreover, recent neuroimaging studies on schizophrenia patients have gradually provided converging evidence elucidating the neural basis of impairments in social cognition. Previous studies in our laboratory have revealed that patients with schizophrenia exhibit impairments in emotion-intensity recognition (Namiki et al., 2007) and emotion-attribution tasks (Fujiwara et al., 2007; Yamada et al., 2007), which are correlated with volume reductions in the amygdala and medial frontal lobes, respectively. As for ToM and empathy impairments in schizophrenia, structural and functional abnormalities have been reported in the left temporoparietal junction (TPJ), temporal pole, medial prefrontal cortex, and left ventrolateral prefrontal cortex (Hirao et al., 2008; Benedetti et al., 2009).

While the neural basis of alexithymia remains a subject of ongoing investigation, previous neuroimaging studies have suggested the importance of the anterior cingulate cortex (ACC), orbitofrontal cortex, dorsolateral prefrontal cortex, and insula in alexithymia in healthy subjects (Kano et al., 2003; Moriguchi et al., 2007b; Borsci et al., 2009). However, the relationship between brain alterations and alexithymia in schizophrenia remains unclear, and so far there have been no studies exploring such a relationship in the whole brain in schizophrenia.

Thus, in this study, we applied the Japanese version of the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994a,b; Moriguchi et al., 2007a) and VBM to elucidate the association between alexithymia and regional GM alterations in patients with schizophrenia. With its relatively high reliability and validity, the TAS-20 is widely used for measuring alexithymia (Moriguchi et al., 2007a), and was used to assess alexithymia in previous studies on patients with schizophrenia (Maggini and Raballo, 2004; Todarello et al., 2005).

We developed three hypotheses for this study: (1) that alexithymia would be detected in patients with schizophrenia, possibly exhibiting a specific pattern; (2) that GM volume reductions would be exhibited in schizophrenia, and specific regional GM alterations would be related to alexithymia in schizophrenia, which reflect the components of alexithymia; and (3) that the latter regions would also overlap with the cortical and subcortical structures that are critical for social cognition.

2. Methods

2.1. Participants

The schizophrenia group comprised 21 patients (14 men and seven women, all right-handed) who were referred to the Department of Psychiatry, 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 (typical [$n = 2$], atypical [$n = 14$], typical and atypical [$n = 5$]), and all were all physically healthy at the time of scanning and cognitive tests. None had a history of neurological injury or disease, severe medical diseases, or substance abuse that may affect brain function.

The control comparison group comprised 24 healthy individuals (16 men and eight women, all right-handed) matched to the schizophrenia group with respect to age, gender, and education level. They were also evaluated using the SCID, and found to have no history of neurological or psychiatric disease, and no first-degree relatives suffering from psychotic episodes. Table 1 presents participants' demographic information.

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

2.2. Basic cognitive tasks

To evaluate participants' basic cognitive abilities, we administered the following tests. The Japanese Version of the National Adult Reading Test (Matsuoka et al., 2006) was used as an index of the premorbid IQ of patients with schizophrenia. In addition, the estimated verbal IQ (VIQ) and performance IQ (PIQ) scores were obtained from vocabulary and block design subtests, respectively, in the Wechsler Adult Intelligence Scale-Revised, by transforming the scores corrected for age into t scores.

2.3. The 20-item Toronto Alexithymia Scale (TAS-20)

The Japanese version of the TAS-20 was used to assess alexithymia. The TAS-20 is a self-report questionnaire for measuring alexithymia by examining three factors: (a) difficulty identifying feelings (DIF); (b) difficulty describing feelings (DDF); and (c) externally oriented thinking (EOT). Each of the 20 items is rated on a five-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores overall and for each of these subscales are indicative of alexithymia.

2.4. MRI acquisition and pre-processing

All participants underwent MRI scans on a 3-Tesla whole-body scanner equipped with an 8-channel phased-array head coil (Trio, Siemens, Erlangen, Germany). The scanning parameters of the T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE = 4.38 ms; TR = 2000 ms; inversion time (TI) = 990 ms; FOV = 225 mm × 240 mm; matrix = 240 × 256; resolution = 0.9375 mm × 0.9375 mm × 1.0 mm; and 208 total axial sections without intersection gaps.

We applied VBM to investigate regional brain volume alterations, using an extension of statistical parametric mapping 5 (SPM5; Wellcome Department of Imaging Neuroscience, London, UK), specifically using the VBM5.1 toolbox (Gaser; http://dbm.neuro.uni-jena.de/vbm) running in Matlab 2007b (MathWorks, Natick, MA, USA) for analyses. Images were normalized and segmented into gray and white matter partitions in the unified segmentation step (Ashburner and Friston, 2005). In SPM5, prior probability maps (modified version of the International Consortium for Brain Mapping [ICBM] Tissue Probabilistic Atlases) are successfully warped to the individual brains, meaning that creating a customized template (used in the so-called 'optimized' VBM protocol) is unnecessary.

The images were re-sliced into 1 mm × 1 mm × 1 mm voxels. Images were modulated by the Jacobian determinants for nonlinear warping only. The modulated GM images were smoothed with a Gaussian kernel of 12-mm full-width at half-maximum, on which all analyses were performed.

2.5. Data analyses

2.5.1. Correlation of TAS-20 score with clinical and cognitive measures

First, independent sample t-tests were applied to examine group differences in basic cognitive tasks and TAS-20 scores. Gender differences in TAS-20 scores were also examined. Second, correlational analyses were performed between TAS-20 total scores and clinical (positive, negative, general psychopathology of PANSS, duration of illness, and medication level) and demographic (age, gender, education level, and IQs) variables. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$ (two-tailed) in all analyses.

2.5.2. Regional GM reductions in patients relative to controls

To identify brain regions in which patients with schizophrenia exhibited 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 covariates of no interest. Because the images were modulated for nonlinear warping only, we did not correct for differences in brain sizes in the statistical model (http://dbm.neuro.uni-jena.de/vbm/segmentation/modulation/). A voxel-level height threshold was set at $P < 0.001$ (uncorrected), in accord with a previous VBM study on alexithymia (Borsci et al., 2009), and an extent threshold of 100 voxels was also applied. Montreal Neurological Institute (MNI) coordinates were transformed into Talairach coordinates (Talairach and Tournoux, 1988) using the mni2tal.m Matlab script written by Matthew Brett (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

2.5.3. Correlational analyses

Correlational analyses were carried out in two ways. First, we performed multiple regressions in SPM5 to explore the brain regions that negatively correlated with the TAS-20 total scores throughout the whole brain in the control group and patient group independently. Age and gender were entered into the model as covariates of