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Manual dexterity and brain structure in patients with schizophrenia: A whole-brain magnetic resonance imaging study

Shinsuke Hidese[a,b], Miho Ota[a], Daimei Sasayama[a], Junko Matsuo[a], Ikki Ishida[a], Moeko Hiraishi[a], Toshiya Teraishi[a], Kotaro Hattori[a], Hiroshi Kunugi[a,b,*]

[a] *Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), 4-1-1, Ogawa-Higashi, Kodaira, Tokyo 187-8502, Japan*

[b] *Department of NCNP Brain Physiology and Pathology, Division of Cognitive and Behavioral Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan*

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ABSTRACT

The Purdue Pegboard Test (PPT) is a motor coordination task used to assess manual dexterity. Although several brain regions are thought to be involved in PPT performance, the relationship of the task with decreased insular volume has not been investigated. The PPT was administered to 83 subjects diagnosed with schizophrenia (mean ± standard deviation age: 38.6 ± 11.2 years; 47 males, 36 females) and 130 healthy controls (42.1 ± 15.2 years; 67 males, 63 females). All subjects were Japanese and right-handed. Gray matter volume was analyzed using voxel-based morphometry in statistical parametric mapping, while white matter measures were analyzed using diffusion tensor imaging in tract-based spatial statistics. For the patients with schizophrenia, the left-hand scores positively correlated with the right insular and bilateral operculum volumes, while the summation score (sum of left-, right-, and both-hands scores) positively correlated with the right insular volume, and the summation and assembly (number of assemblies completed) scores correlated with the diffuse white matter fractional anisotropy, axial diffusivity, and radial diffusivity values. In contrast, no significant correlations were found for the controls. These results suggested that decreased insular volume and white matter measures contributed to the impairments in manual dexterity observed in subjects with schizophrenia.

1. Introduction

Patients with schizophrenia exhibit impairments in a variety of cognitive functions, including fine motor (e.g., manual) dexterity (Ayesa-Arriola et al., 2013; Gonzalez-Blanch et al., 2007; Heinrichs and Zakzanis, 1998; Midorikawa et al., 2008; Sponheim et al., 2010). The Purdue Pegboard Test (PPT) is a bimanual coordination task that can be used to assess psychomotor abilities (i.e., motor speed and coordination) in subjects, such as patients with schizophrenia (Lee et al., 2013). PPT scores are consistently lower in patients with schizophrenia compared with healthy controls (Docx et al., 2013; Fuller and Jahanshahi, 1999; Galderisi et al., 2009). We have also reported that patients with schizophrenia have lower PPT scores, and these deficits might have been worsened by the negative influence of psychotropic medications (Sasayama et al., 2014). Moreover, associations between bimanual dexterity impairments and daily functioning have been reported in patients with schizophrenia (Lehoux et al., 2003; Lin et al., 2015).

The neural basis of the sensory-motor control of manual dexterity in the cerebral cortices of primates has been documented (Darian-Smith et al., 1996; Lemon, 1999). In healthy humans, deep and periventricular white matter hyperintensities were found to be related to fine motor disabilities detected using the PPT in 60–64-year-old individuals (Sachdev et al., 2005). The age-related atrophy of thalamic subregions has also been suggested to contribute to decreased PPT performance in 20–79-year-old participants (Serbruyns et al., 2015). Decreased manual dexterity performance on the Grooved Pegboard Test, which is a unilateral motor task, is associated with bilateral decreases in cerebellar gray and white matter volumes in individuals over 65 (Koppelmans et al., 2015).

Patients with schizophrenia are known to exhibit neurocognitive

Abbreviations: AD, axial diffusivity; ANCOVA, analysis of covariance; CPeq, chlorpromazine-equivalent doses; DTI, diffusion tensor imaging; FA, fractional anisotropy; FWE, family-wise error; MANCOVA, multivariate analysis of covariance; MRI, magnetic resonance imaging; NCNP, National Center of Neurology and Psychiatry; PANSS, Positive and Negative Syndrome Scale; PPT, Purdue Pegboard Test; RD, radial diffusivity; VBM, voxel-based morphometry

* Corresponding author at: Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1, Ogawa-Higashi, Kodaira, Tokyo 187-8502, Japan.

E-mail address: hkunugi@ncnp.go.jp (H. Kunugi).

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impairments, including fine motor impairments, due to aberrant structure and function of the motor cortices, basal ganglia, thalamus, cerebellum, and, especially, the white matter tracts connecting them (Walther, 2015; Walther and Strik, 2012). The PPT is thought to reflect fine motor or basal ganglia function (Heinrichs and Awad, 1993), and frontal/subcortical circuitry is thought to be involved in the test performance in patients with schizophrenia and neurological soft signs (Flashman et al., 1996). A study using voxel-based diffusion tensor imaging (DTI) reported decreased white matter fractional anisotropy (FA) values in the forceps minor, inferior fronto-occipital fasciculus, anterior thalamic radiation, and corticospinal and corticopontine tracts of patients with first-episode psychosis, and these changes corresponded with poor performance on the Grooved Pegboard Test (Perez-Iglesias et al., 2010). For the white matter, DTI studies have revealed disturbances in white matter microstructure in many brain regions in patients in various phases of the course of schizophrenia (Karlsgodt, 2016; Kyriakopoulos et al., 2008).

A meta-analysis has shown that insular volume is decreased in patients with schizophrenia (Shepherd et al., 2012). Although manual dexterity performances were not reported, the insular cortex has been associated with sensory-motor function in humans (Augustine, 1996), including psychiatric patients (Nagai et al., 2007). Furthermore, reports of abnormal hemisphere asymmetry and connectivity in subjects with schizophrenia (Oertel-Knochel et al., 2012; Ribolsi et al., 2014) have suggested that the neurostructural bases of the dominant and non-dominant hand PPT scores differ between patients with schizophrenia and healthy individuals.

Although the profile and anatomical background of the PPT in patients with schizophrenia as well as healthy subjects have been presented, the relationship of the test scores and brain structure has not been studied, except in cases of healthy children and/or adolescents (Kuhn et al., 2012; Kurth et al., 2013; Pangelinan et al., 2011). Based on previous findings, we hypothesized that manual dexterity and brain structure would be associated in patients with schizophrenia and healthy adults. Furthermore, considering lower PPT scores and disturbed gray and white matter measures in patients with schizophrenia, we hypothesized that there are structural abnormalities of the brain associated with manual dexterity, which are characteristic to the patients. We used voxel-based morphometry (VBM) and DTI to investigate these hypotheses. No specific regions were examined because of a previous DTI study of manual dexterity in adults that utilized a whole-brain method (Perez-Iglesias et al., 2010).

2. Methods

2.1. Subjects

The subjects used in this study were 83 patients with schizophrenia (mean ± standard deviation age: 38.6 ± 11.2 years; 47 males, 36 females) and 130 healthy controls (mean ± standard deviation age: 42.1 ± 15.2 years; 67 males, 63 females) who were matched for age, sex, and ethnicity (Japanese). All subjects were self-reported right-handers who were enrolled via recruitment forms at the National Center of Neurology and Psychiatry (NCNP) Hospital, advertisements in a free local magazine, or announcements on our website. The subjects were screened for axis I psychiatric disorders using the Japanese version of the Mini-International Neuropsychiatric Interview (Otsubo et al., 2005; Sheehan et al., 1998), which was executed by board-certificated psychiatrists. The patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition criteria (American Psychiatric Association, 1994) based on the results of the Mini-International Neuropsychiatric Interview and medical records, if available. None of the healthy controls had axis I psychiatric disorders or never received psychiatric services. Both patients and controls with a medical history of neurological diseases, severe head injury, substance abuse, or mental retardation were excluded. All subjects signed an informed consent form after the study was explained to them. The study protocol was approved by the ethics committee of the NCNP and compiled in accordance with the Declaration of Helsinki (World Medical Association, 2013).

2.2. Clinical and psychological assessments

Manual dexterity was assessed by the PPT (Tiffin and Asher, 1948); Model 32020, Lafayette Instrument Company, Lafayette, IN, USA), as described elsewhere (Sasayama et al., 2014). The PPT results are comprised of five separate scores (i.e., left-hand, right-hand, both-hands, summation, and assembly scores). A Purdue Pegboard has two vertical arrays of 25 holes on the right- and left-sides. From the right to the left, the upper 4 cups contain 25 pegs, 20 collars, 40 washers, and 25 pegs, respectively. The left- and right- hand scores refer to the number of pegs that were correctly placed in the holes within 30 s using the left and right hands, respectively. The both-hands score refers to the number of pairs of pins that were correctly placed in the holes within 30 s using both hands. The summation score is the sum of the left-, right-, and both-hands scores, while the assembly score is the number of assemblies completely constructed with a peg, washer, collar, and another washer using both hands alternately within 60 s. The summation and assembly scores are indices of gross and fine fingertip dexterity, respectively. The symptom severities of the patients with schizophrenia were assessed by board-certified psychiatrists using the Japanese version of the Positive and Negative Syndrome Scale (PANSS; (Igarashi et al., 1998; Kay et al., 1987). The psychiatrists had been trained to conduct the PANSS, but their inter-rater reliability was not calculated. The patients' daily doses of antipsychotics were converted to chlorpromazine-equivalent doses (CPeq), as described in a previous Japanese guideline (Inada and Inagaki, 2015).

2.3. Statistical analyses

Continuous and categorical variables were compared between the patient and control groups using unpaired t-tests and chi-square tests, respectively. Correlations of the continuous and categorical variables were calculated using Pearson's and Spearman's correlation coefficients, respectively. Differences in the PPT scores between the groups were assessed using a one-way multivariate analysis of covariance (MANCOVA) and a two-way analysis of covariance (ANCOVA) (group [schizophrenia/control] x side [left/right hand]) that were controlled for age and sex, because sex differences have been reported previously (Peters et al., 1990). Bonferroni corrections were applied to correct for the multiple testing of five separate PPT scores in the correlational and MANCOVA analyses. The effect sizes were calculated using Cohen's d for the t-test, φ for the chi-square test, and η^2 for the MANCOVA. The statistics were computed by using the Statistical Package for the Social Sciences (version 24.0; IBM Japan, Ltd., Tokyo, Japan). All statistical tests were two-tailed, and p values less than 0.05 were considered significant.

2.4. Magnetic resonance imaging (MRI) data acquisition and processing

Three-dimensional T1-weighted images and DTI data were obtained with high spatial resolution using a Magnetom Symphony 1.5 T system (Siemens Healthcare GmbH, Erlangen, Germany). The VBM analyses were performed using Christian Gaser's toolbox (http://dbm.neuro.uni-jena.de/vbm8/) in the Statistical Parametric Mapping software package (version 12, http://www.fil.ion.ucl.ac.uk/spm). To label the brain regions, we used the coordinates of the Montreal Neurological Institute 152 space that is included in the Statistical Parametric Mapping software. Gray matter images were smoothed using an 8-mm full-width at half-maximum Gaussian kernel. The level of statistical significance was set to a peak value of $p < 0.05$ [family-wise error (FWE) corrected] and a cluster level of $p < 0.05$ (FWE corrected). The DTI scans were