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Discrimination between schizophrenia and major depressive disorder by magnetic resonance imaging of the female brain

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ABSTRACT

Background: Although schizophrenia and major depressive disorder (MDD) differ on a variety of neuroanatomical measures, a diagnostic tool to discriminate these disorders has not yet been established. We tried to identify structural changes of the brain that best discriminate between schizophrenia and MDD on the basis of gray matter volume, ventricle volume, and diffusion tensor imaging (DTI).
Method: The first exploration sample consisted of 25 female patients with schizophrenia and 25 females with MDD. Regional brain volumes and fractional anisotropy (FA) values were entered into a discriminant analysis. The second validation sample consisted of 18 female schizophrenia and 16 female MDD patients.
Results: The stepwise discriminant analysis resulted in correct classification rates of 0.80 in the schizophrenic group and 0.76 in MDD. In the second validation sample, the obtained model yielded correct classification rates of 0.72 in the schizophrenia group and 0.88 in the MDD group.
Conclusion: Our results suggest that schizophrenia and MDD have differential structural changes in the examined brain regions and that the obtained discriminant score may be useful to discriminate the two disorders.

1. Introduction

Major depressive disorder (MDD) is a common disorder with a lifetime prevalence reported to range from 8% to 12% in almost every country worldwide (Andrade et al., 2003). Schizophrenia is also common and reported to be ranged from 0.16% to 1.21% (Saha et al., 2005). Depression manifested in 21% to 74% of acute patients with recent onset schizophrenia and in 13% to 50% of those with chronic schizophrenia, while depressive features were found in even greater rates, up to 80%, in schizophrenia (Kollias et al., 2008). These data indicate that discrimination between schizophrenia and MDD is often difficult in the clinical setting.

Many magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) studies have focused on structural brain abnormalities in schizophrenia and MDD. In schizophrenia, evidence has been obtained showing changes in the frontal and temporal lobes, thalamus, anterior cingulate cortex (ACC), and corpus callosum, and showing dilatation of the Sylvian fissure and the third ventricle (reviewed by Arnone et al., 2009; Glahn et al., 2008; Honea et al., 2005; White et al., 2008). In MDD, changes in the frontal and temporal lobes, cingulum, and the subcortical structures have been reported (Arnone et al., 2012; Bora et al., 2012; Sexton et al., 2009).

Some studies have attempted to discriminate between patients with schizophrenia and healthy subjects using brain anatomical structures obtained by MRI (Leonard et al., 1999; Nakamura et al., 2007; Takayanagi et al., 2010). Other studies including ours reported an unbiased, rater-independent technique known as the voxel-based morphometry (VBM)-based classification approach (Davatzikos et al., 2005; Kawasaki et al., 2007; Ota et al., 2012). Each of these studies showed a fair to excellent classification rate. Additionally, one study evaluated the effectiveness of the structural neuroanatomy derived from MRI images as a diagnostic marker of MDD, and showed a relatively low classification rate (Costafreda et al., 2009). However, to our knowledge, there has been no

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attempt to produce an MRI-based diagnostic tool to objectively discriminate between schizophrenia and MDD.

Functional MRI and DTI have revealed the fine neural networks in the central nervous system (CNS). Together the thalamus, insula, ACC, and corpus callosum are regarded as the central relay station in the brain, and they can be subdivided into functionally different clusters (Buchsbaum et al., 1996; Makris et al., 2006; McCormick et al., 2006; Witelson, 1989). Several studies have detected subdivided region-specific brain changes for schizophrenia and MDD (Buchsbaum et al., 1996; Coryell et al., 2005; Crespo-Facorro et al., 2000; Makris et al., 2006; Mitelman et al., 2009). However, previous neuroimaging studies conducted to discriminate between schizophrenia and control and between MDD and controls paid little attention to these divisions. Moreover, the robust change of the ventricle size was known to be useful to distinguish the bipolar patients from schizophrenia patients (reviewed by Arnone et al., 2009). Then, it would be suitable to add the ventricles for variables of discriminant analysis between MDD and schizophrenia.

We hypothesized that the characteristic distribution of regional brain changes, especially in the limbic system and ventricles, in schizophrenia patients could have diagnostic value in that it could be used to discriminate individuals with schizophrenia from those with MDD.

2. Methods

2.1. Participants

The analysis proceeded in two stages. The first analysis was conducted to produce a statistical model to classify subjects according to the current diagnostic system, and the second analysis was performed to validate the statistical model by classifying a new cohort.

Toward this end, subjects were assigned to two independent groups based on the timing of their participation. The first exploration sample consisted of 25 patients with schizophrenia and 25 with MDD. Consensus diagnosis by at least two psychiatrists was made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association 1994). The second validation sample consisted of 18 patients with schizophrenia and 16 with MDD. All subjects were Japanese females and biologically unrelated to each other. Exclusion criteria included a history of head injury, central nerve system disease, speech or hearing difficulties, significant cerebrovascular diseases (cortical infarctions, multiple lacunar lesions or leukoaraiosis), and fulfillment of the DSM-IV criteria for abuse of illicit drugs or alcohol at any point during their lifetime. Further, to avoid the co-morbidity of the psychiatric illness, the schizophrenic patients treated with antidepressants were excluded from the study. The psychopathological state of all of the schizophrenia subjects was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), and the patients with MDD were rated with the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) for their depressive symptoms. Daily doses of antipsychotics including depot antipsychotics and antidepressants were converted to chlorpromazine and imipramine equivalents, respectively using published guidelines (American Psychiatric Association 1997; Inagaki et al. 1999). The study protocol was approved by the ethics committee of the National Center of Neurology and Psychiatry, Japan, and written informed consent for participation in the study was obtained from all subjects.

2.2. MRI data acquisition and processing

MR studies were performed on a Magnetom Symphony 1.5-tesla (Siemens, Erlangen, Germany). Three-dimensional (3D) T1-weighted images were scanned in the sagittal plane (echo time [TE]/repetition time [TR], 2.64/1580 ms; flip angle, 15 degrees; slab thickness, 177 mm; matrix, 208 × 256; number of excitations [NEX] = 1, field of view [FOV], 256 × 315 mm^2; slice thickness, 1.23 mm) yielding 144 contiguous slices through the head. The raw 3D T1-weighted volume data were transferred to a workstation, and structural images were analyzed using Statistical Parametric Mapping 8 (SPM8) software (Wellcome Department of Imaging Neuroscience, London, UK) running on MATLAB 7.0 (Math Works, Natick, MA). First, each individual 3D-T1 image was normalized with the diffeomorphic anatomical registration using exponentiated lie (DARTEL) registration method (Ashburner 2007). Normalized segmented images were modulated by multiplication with Jacobian determinants of the spatial normalization function to encode the deformation field for each subject as tissue density changes in normal space. Gray matter volume images and the cerebrospinal fluid (CSF) images were smoothed using a 12-mm full-width at half-maximum of an isotropic Gaussian kernel.

DTI was performed in the axial plane (TE/TR, 106/11, 200 ms; FOV, 240 × 240 mm^2; matrix, 96 × 96; 75 continuous transverse slices; slice thickness 2.5 mm with no interslice gap). To enhance the signal-to-noise ratio, acquisition was repeated two times. Diffusion was measured along 12 noncollinear directions using a diffusion-weighted factor b in each direction for 1000 s/mm^2, and one image was acquired without using any diffusion gradient. The DTI data sets were analyzed using the DtiStudio program (Jiang et al., 2006). The diffusion tensor parameters were calculated on a pixel-by-pixel basis, and the FA and $b = 0$ image were calculated according to Wakana et al. (2004). FA images were normalized to the standard space. First, each individual 3D-T1 image was coregistered and resliced to its own $b = 0$ image. Next, the coregistered 3D-T1 image was normalized with the DARTEL registration method using SPM8. Finally, the transformation matrix was applied to the FA map. Each map was then spatially smoothed with a 6-mm full-width at half-maximum Gaussian kernel in order to decrease spatial noise and compensate for the inexactitude of normalization.

2.3. Regions of interest

The insula was divided into anterior and posterior parts (Fig. 1a), the thalamus into five subregions (Fig. 1b), the ACC into four subregions (Fig. 1c), and the corpus callosum into six subregions (Fig. 1d). The detailed descriptions of these subregions are given in the Supplementary Information. The Regions of interest (ROIs) of 3rd, 4th, and lateral ventricle were derived from the WFU_pickatlas, extension program of SPM8 (Maldjian et al., 2003, 2004). ROIs were operationally defined on the standard brain of the SPM8, “avg152T1.nii” image. FA values, gray matter volume and ventricle size were both calculated for these ROIs. The boundaries of these ROIs were manually determined using MRIcro (Chris Rorden, University of Nottingham, Nottingham, Great Britain).

2.4. Statistical analysis

Discriminant function analyses were conducted to assess the ability of combinations of brain anatomical variables to distinguish between patients with schizophrenia and those with MDD. The independent variables were the regional gray matter and ventricle volumes/whole brain volume and FA values derived from each normalized individual image by the ROI method using the software MarsBar (Brett et al., 2002). We regarded the gray matter volume plus white matter volume as the whole brain volume. The values of gray and white matter volumes of individual subjects were extracted with the Easy Volume toolbox (http://www.sbirc.ed.ac.uk/LCL/LCL_M1.html) (Pernet et al., 2009) running on Matlab 7.0.