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Research report

Microstructural abnormalities in anterior callosal fibers and their relationship with cognitive function in major depressive disorder and bipolar disorder: A tract-specific analysis study

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ABSTRACT

Background: The corpus callosum modulates interhemispheric communication and cognitive processes. It has been suggested that white matter abnormalities in the corpus callosum are related to the pathophysiology of major depressive disorder (MDD) and bipolar disorder (BD). The aim of this study was to examine microstructural abnormalities in callosal fibers separated by their connection to functional brain regions and determine the relationship of these abnormalities with cognitive function in MDD and BD.

Methods: The subjects were 18 patients with MDD, 20 patients with BD, and 21 healthy controls. The callosal fibers were divided into 6 segments based on their cortical projection using tract-specific analysis of diffusion tensor imaging. We examined differences in the fractional anisotropy (FA) of callosal fibers in six segments among the three subject groups and examined the correlation between the FA in each segment and cognitive performance in the 3 groups.

Results: The FA of anterior callosal fibers were reduced significantly in the MDD and BD groups compared to those in the HC group, and the FA of anterior callosal fibers correlated significantly with the raw scores of the digit sequencing task and symbol coding in the MDD group.

Limitations: The patients were medicated at the time of scanning, and the MDD and BD groups were not matched for symptom severity.

Conclusions: Our results suggest that MDD and BD have similar microstructural abnormalities in anterior callosal fibers connecting bilateral frontal cortices, and these abnormalities may be related to impairment of working memory and attention in MDD.

1. Introduction

Many studies have implicated white matter (WM) abnormalities in the pathophysiology of major depressive disorder (MDD) and bipolar disorder (BD) (Mahon et al., 2010; Nortje et al., 2013; Sexton et al., 2009). WM fibers connect the cortices to each other, and they support the organization of a complex structural and functional network in the brain (Fields, 2008; Paus et al., 2001, 2014). The corpus callosum (CC) is the largest WM tract, and connects the two cerebral hemispheres, allowing interhemispheric communication (Aboitiz et al., 1992a; Doron and Gazzaniga, 2008; Glickstein and Berlucchi, 2008). Hemispheric asymmetries play an important role in the human brain (Aboitiz et al., 1992b; Doron and Gazzaniga, 2008; Van der Knaap and van der Ham, 2011), and abnormalities in the callosal fibers have been suggested as a basis for the neural pathophysiology observed in MDD and BD (Bellani et al., 2009; Savitz and Drevets, 2009; Xu et al., 2013).

WM microstructural abnormalities can be detected by diffusion tensor imaging (DTI). DTI is a noninvasive magnetic resonance imaging (MRI) technique that measures the random motion of water molecules on a microscopic scale and provides information concerning the size, shape, orientation, and geometry of brain tissue (Le Bihan, 2003). In recent years, two main methods of analyzing DTI data are voxel-wise statistical analysis and tract-specific analysis (Paus et al., 2014; Sexton et al., 2009). Meta-analysis of whole-brain DTI studies using voxel-wise statistical analyses reported various WM abnormalities including abnormalities in the CC in

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MDD (Liao et al., 2013) and BD patients (Vederine et al., 2011). However, voxel-wise statistical analyses cannot directly localize deficits to specific tracts and do not provide information on the structural connectivity of fiber tracts between different brain regions. On the other hand, tract-specific analysis can reconstruct WM fibers in vivo and provide information on structural connectivity between distant brain regions, which may be helpful in exploring specific connections that are impaired (Basser et al., 2000; Conturo et al., 1999; Mori et al., 1999). In addition, recent tract-specific analytical studies have developed reproducible analyses to segment the CC based on cortical projection zones (Huang et al., 2005; Lebel et al., 2010). Thus, information on local structural connectivity related to how tracts are connected between functional brain regions can be obtained.

The anterior callosal fibers connect between the bilateral frontal cortices (Barbas and Pandya, 1984), including the cortices associated with several cognitive domains such as memory, attention, and executive function (Duncan and Owen, 2000). Cognitive impairment has been observed in MDD and BD (Millan et al., 2012; Xu et al., 2012), and it occurs not only during affective episodes, but also into the euthymic phase of illness (Porter et al., 2007; Arts et al., 2008). Callosal fibers modulate interhemispheric communication and cognitive processes (Doron and Gazzaniga, 2008; Glickstein and Berlucchi, 2008). Therefore, microstructural abnormalities of the anterior callosal fibers may be related to cognitive impairment.

In this study, we examined differences in the microstructural abnormalities of callosal fibers in 6 tract segments based on cortical projection zones between patients with MDD and BD and in healthy controls using tract-specific analysis of DTI, and correlations between the microstructural abnormalities of callosal fibers in each segment and cognitive performance in the 3 groups. We hypothesized that patients with MDD and BD have similar microstructural abnormalities in callosal fibers connecting between the bilateral frontal cortices, and that abnormalities in the anterior callosal fibers correlate with cognitive impairments.

2. Subjects and methods

2.1. Subjects

The demographic and clinical characteristics of the study subjects are shown in Table 1. The subjects were healthy controls (HC group; $n=21$) and patients with MDD (MDD group; $n=18$) and BD (BD group; $n=20$). The subjects ranged in age from 29 to 62 years. We excluded patients with a co-morbid psychiatric, neurological, or medical illness, and substance or alcohol abuse. We assessed the symptom severity of the patients using the Hamilton Rating Scale for Depression-17 items (HAMD) and the Young Mania Rating Scale (YMRS). The intelligence quotient of all subjects was estimated with the Japanese Adult Reading Test (JART). All patients, except one MDD subject, took a range of medications, including lithium, antidepressants, anticonvulsants, and antipsychotics. Experienced psychologists performed neurocognitive tests to all subjects. The tests were selected to examine frontal cognitive functions: digit sequencing task (working memory), symbol coding (attention), list learning (verbal memory), and Tower of London (executive function). This study was approved by the Ethics Committee of Wakayama Medical University and written informed consent was obtained from all of the subjects.

2.2. MRI data acquisition

All MR imaging examinations were performed using a 3.0 T MR scanner (Achieva TX 3.0 T; Philips Medical Systems, Best, The Netherlands) with a 32-element sensitivity encoding head coil. DTI was performed with a single-shot spin-echo echoplanar imaging diffusion sequence in 15 directions. The DTI scan duration was 4 min 4 s with 935 images obtained. Other DTI parameters included TR/TE=6421/69 ms, FOV=224 mm, flip angle=90 deg, 55 slices, acquisition voxel size=2.0 × 2.0 × 2.5 mm, slice thickness=2.5 mm, slice gap=0 mm, and 2b-values of 0 and 1000. For anatomic MRI, T1-weighted 3D-fast field-echo imaging was obtained. The T1-weighted 3D-fast field-echo imaging studies were obtained in the sagittal plane with a duration of 5 min. The MRI parameters were TR/TE=7.0/3.3 ms, FOV=220 mm, flip angle=10 deg, 210 slices, acquisition voxel size=0.86 × 0.86 × 0.9 mm, effective reconstructive voxel size=0.76 × 0.76 × 0.9 mm, and a slice thickness=0.9 mm.

2.3. DTI data processing

Information on WM diffusion can be evaluated by some DTI-derived data, such as fractional anisotropy (FA) and the apparent diffusion coefficient (Basser and Pierpaoli, 1996). We used FA, which measures the degree of water diffusion anisotropy on a scale from zero to one, to characterize WM microstructural abnormalities (Basser and Pierpaoli, 1996). DTI data were analyzed using a Philips Extended Workspace (EWS, Release 2.6.3.1; Philips, Best, The Netherlands). FA thresholds to initiate and continue tracking were set to 0.2. The maximum angle threshold was 50 deg. Tractography was performed using the two regions-of-interest (ROIs) approach. The ROI locations and exclusion criteria were described by previous tract-specific analysis studies (Huang et al., 2005; Lebel et al., 2010). One region was drawn on a midsagittal slice encompassing the entire CC, and 6 separate ROIs spanning both sides of the midline were used as target regions to segment the CC into distinct sections. All ROIs were drawn according to specific anatomical landmarks and guidelines were followed carefully and consistently for each individual. The callosal fibers were separated into 6 segments based on their cortical projection zones, as shown in Fig. 1. From anterior to posterior, the six sections were: orbital frontal (OF), anterior frontal (AF), superior frontal (SF), parietal (Par), temporal (Temp), and occipital (Occ). Fibers that were clearly not part of the anatomical connectivity of the track were eliminated. FA was calculated for each region by averaging all voxels over the entire tract.

2.4. Statistics

All statistical analyses were performed using SPSS 11.0J for Windows (SPSS Japan Inc., Japan). Analysis of variance (ANOVA) was used to examine differences in age, JART score, and each score of neurocognitive tests between the three groups, with significance set at $p<0.05$. χ^2 test was used to examine differences in gender distribution between the three groups, with significance set at $p<0.05$. Independent samples t-test was used to examine differences in duration of illness and scores of the HAMD and YMRS between the MDD and BD groups, with significance set at $p<0.05$. The repeated measures ANOVA and the Bonferroni's post hoc test was used to examine differences in the FA of callosal fibers in each segment between the three groups, with significance set at $p<0.05$. In the three groups, correlations between the FA of callosal fibers in each segment and the raw scores of neurocognitive tests were analyzed using Spearman's rank correlation test, with significance set at $p<0.05$. To exclude the possibility of any confounding factors, exploratory analysis using Spearman's rank correlation test was also carried out between the FA of callosal fibers in each segment and clinical characteristics (age, duration of illness, scores of the HAMD, YMRS and JART) in the MDD and BD groups.