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Widespread white matter microstructural abnormalities related to cognitive impairment in major depressive disorder: A tract-based spatial statistics study

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Abstract

White matter (WM) microstructural abnormalities have been observed in patients with major depressive disorder (MDD). Using tract-specific analysis (TSA) of diffusion tensor images on carpus callosum, we previously reported that WM microstructural abnormalities in the anterior callosal fiber was related to impaired working memory and attention in patients with MDD. In this study, we examined whole-brain WM microstructural abnormalities and their relationship with working memory and attention in patients with MDD using tract-based spatial statistics (TBSS). We analyzed diffusion tensor image data and scores of digit sequencing task (working memory) and symbol coding (attention) from our previous TSA study (21 healthy controls (HC) and 18 patients with MDD). Using TBSS, we examined differences in fractional anisotropy (FA) of whole-brain WM between the MDD and HC groups, and examined the correlations between FA and scores of digit sequencing task and symbol coding in the MDD group. Compared to the HC group, the FA of WM was significantly reduced in patients with MDD in widespread regions, which correlated with the poorer performance on the digit sequencing task and symbol coding. Our results suggested widespread WM microstructural abnormalities, which were associated with the impairment of working memory and attention in patients with MDD.

Highlights:

- We examined whole-brain WM microstructural abnormalities in MDD.
- We performed statistical analysis of FA with tract-based spatial statistics of DTI.
- The FA of WM in widespread regions was significantly reduced in MDD.
- Reduce FA was significantly related with cognitive impairment in MDD.
- This study contributes to the understanding of WM pathophysiology in MDD.

Key words:

Cognitive impairment; Diffusion tensor imaging; Major depressive disorder; Tract-based spatial statistics; White matter pathophysiology

Abbreviations:

CC, corpus callosum; DTI, diffusor tensor imaging; FA, fractional anisotropy; FSL, FMRIB software Library; HAMD, Hamilton Rating Scale for Depression; HC, healthy controls; JART, Japanese Adult Reading Test; MDD, major depressive disorder; TBSS, tract-based spatial statistics; TSA, tract-specific analysis; WM, white matter

1. Introduction

Major depressive disorder (MDD) is a globally prevalent psychiatric disorder that causes great social burden (Kupfer et al., 2012; Mathers et al., 2008). Extensive evidence suggests that cognitive impairment in MDD, which is related to psychosocial and functional outcomes (Evans et al., 2014; McIntyre et al., 2013), occurs not only during affective episodes, but also during the euthymic phase of the condition (Porter et al., 2007; Rock et al., 2014). However, the pathophysiology of cognitive impairment in MDD has not been well elucidated. Since many studies have implicated microstructural abnormalities of the white matter (WM) in the pathophysiology of MDD, it is an area that has been receiving increased attention (Jiang et al., 2016; Liao et al., 2013). WM fibers structurally and functionally connect cortical and sub-cortical regions to each other (Sexton et al., 2009; Wise et al., 2016), including the cortices associated with several cognitive domains (Baars et al., 2013; Duncan and Owen, 2000).

Diffusion tensor imaging (DTI) is one tool that allows the quantitative assessment of WM microstructural abnormalities. Two main analytical techniques, namely, tract-specific analysis (TSA) and tract-based spatial statistics (TBSS), have been used in conjunction with DTI. TSA is used to estimate microstructural abnormalities that are specific to WM tracts (Mori et al., 1999), while TBSS is used for whole-brain analysis (Smith et al., 2006). The advantage of TSA is its ability to estimate WM microstructural abnormalities between cerebral cortices in the native space of each person studied. Thus, information on the association between local structural connectivity and the connection of tracts between functional brain regions can be obtained (Mori et al., 1999). Conversely, TBSS is advantageous because it enables the exploratory investigation of the whole brain, as it does not require regions of interest to be specified *a priori* (Smith et al., 2006). Recent DTI studies have employed simultaneous TSA and TBSS; abnormalities that are found using both

techniques are considered to be more robust and reproducible (Kamagata et al., 2013, Shimoji et al., 2013). However, to our knowledge, no previous studies have investigated WM microstructural abnormalities in MDD using both TSA and TBSS.

Using TSA, we previously reported microstructural abnormalities in the fiber bundle connecting the left and right frontal cortices via the anterior corpus callosum (CC), and significant relationship between those microstructural abnormalities and impairment of working memory and attention in patients with MDD (Yamada et al., 2015). In order to gain better understanding of the pathophysiology of cognitive impairment in MDD, we examined the relationship between whole-brain WM microstructural abnormalities and cognitive impairment in patients with MDD, using diffusion tensor image data and scores of neurocognitive tests from our previous TSA study (Yamada et al., 2015).

2. Methods

2.1. Subjects

The demographic and clinical characteristics of the study subjects are shown in Table 1. The subjects were 21 healthy controls (HC) and 18 patients with MDD (Table 1). The subjects with MDD were recruited from outpatients of the Wakayama Medical University Hospital and HC were recruited from the hospital staffs. The MDD group diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. We excluded patients with co-morbid psychiatric, neurological, or medical illness, as well as substance or alcohol abuse. The severity of symptoms of patients with MDD was assessed using the 17-item Hamilton Rating Scale for Depression (HAMD). The intelligence quotient of each subject was estimated with the Japanese Adult Reading Test (JART). Apart from one patient, all patients with MDD were being treated with various medications, including antidepressants, mood stabilizers, and antipsychotics. Cognitive function of each subject was

assessed by experienced psychologists using a 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 the subjects.

2.2. Magnetic resonance imaging data acquisition

All magnetic resonance imaging (MRI) examinations were performed using a 3.0T MR scanner (Achieva TX 3.0T; 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 duration of each DTI scan was 4 min and 4 s, and a total of 935 images were obtained. The other DTI parameters were as follows: TR/TE = 6421/69 ms, FOV = 224 mm, flip angle = 90º, 55 slices, acquisition voxel size = 2.0 x 2.0 x 2.5 mm, slice thickness = 2.5 mm, slice gap = 0 mm, and 2b-values of 0 and 1000. For anatomic MRI, 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 as follows: TR/TE = 7.0/3.3 ms, FOV = 220 mm, flip angle = 10º, 210 slices, acquisition voxel size = 0.86 x 0.86 x 0.9 mm, effective reconstructive voxel size = 0.76 x 0.76 x 0.9 mm, and a slice thickness = 0.9 mm.

2.2. Image analysis

DTI data were processed using the FMRIB software Library (FSL) version 5.0.5 (Smith et al., 2004) and TBSS (Smith et al., 2006). The Brain Extraction Tool was used to create a binary mask from the non-diffusion weighted data, and diffusion tensor-associated parameters, such as fractional anisotropy (FA), were calculated using the DTIFIT program in the FSL. Non-linear transformation and affine registration were performed to normalize all

FA data into a standard space using the nonlinear registration tool, FNIRT. Normalized FA images were averaged to create a mean FA image, and a mean FA skeleton was created by taking the centers of all tracts that were common to all subjects. The voxel values of each subject's FA map were projected onto the skeleton by searching the local maxima along the perpendicular direction from the skeleton.

2.3. Statistical Analyses

We performed pair-wise two-sample *t*-tests between the MDD and HC groups based on a voxel-wise permutation-based non-parametric inference using the *Randomize* program implemented in FSL, with age and gender as a nuisance covariate. Using threshold-free cluster enhancement, *Randomize* performed 5,000 permutations. The threshold was set at $p < 0.05$, corrected for multiple comparisons using family-wise error. For the MDD group, *Randomize* was also used to examine the relationship between FA and clinical characteristics (i.e., age, duration of illness, and the HAMD and JART scores) and the raw score of neurocognitive tests with multiple linear regression analysis ($p < 0.05$, corrected for multiple comparisons, age at the time of the MRI scan).

3. Results

The age, gender, JART score, and raw score of the Tower of London did not significantly differ between the MDD and HC groups (Table 1). The raw scores of the digit sequencing task, symbol coding, and list learning, however, significantly differed between the groups. The FA of WM in widespread regions was significantly reduced in the MDD group, compared to the HC group (Fig. 1). In the MDD group, reduced FA was significantly correlated with poorer performance on digit sequencing task and symbol coding (Fig. 2). FA did not correlate significantly with age, duration of illness, HAMD and JART scores, or the

raw scores of the list learning and Tower of London.

4. Discussion

In this study, we examined whole-brain WM microstructural abnormalities and their relationship with cognitive impairment in patients with MDD using TBSS. Compared to the HC group, the FA of WM was significantly reduced in patients with MDD in a number of regions, which correlated with the poorer performance on the digit sequencing task and symbol coding. Our results suggested that patients with MDD have widespread WM microstructural abnormalities, which may be related to the impairment of working memory and attention.

The present study applied TBSS to DTI data from our previous TSA study (Yamada et al., 2015), which demonstrated the reduced mean FA of the WM fiber bundle connecting the bilateral frontal cortices via the anterior CC in the MDD group (Yamada et al., 2015). The current TBSS study demonstrated that FA of WM in a number of regions, including the anterior CC, was significantly reduced in the MDD group, when compared with the HC group. The reduced FA of the anterior CC corroborated with the findings from a recent meta-analysis of whole-brain DTI studies (Wise et al., 2016). TSA is advantageous since it assesses how local structural connectivity is related to the tracts that connect functional brain regions (Mori et al., 1999), while TBSS is advantageous because it enables an exploratory investigation of the whole brain (Smith et al., 2006). A DTI study employing both TSA and TBSS would provide more detailed information regarding local and global WM microstructural abnormalities (Kamagata et al., 2013). The current TBSS study demonstrated that FA was not only reduced in the anterior CC, but also in other brain region, suggesting widespread WM microstructural abnormalities in patients with MDD.

Further, there was a significant correlation between reduced FA and poorer

performance on digit sequencing task and symbol coding in the MDD group. To perform the digit sequencing task, the ventrolateral prefrontal cortex initially receives information from posterior association areas. Then, the dorsal lateral prefrontal cortex is recruited for the manipulation of this information (Walter et al., 2003; Werheid et al., 2002). A meta-analysis of functional MRI studies in patients with MDD demonstrated the hyperactivity of the left hemisphere and hypoactivity of the right hemisphere during working memory tasks (Wang et al., 2015). Although the relationship between WM microstructural abnormalities and cerebral activity has not been investigated much, one study, which utilized TBSS and resting state functional MRI, reported a significant positive correlation between FA in the right anterior CC and functional connectivity of the right orbitofrontal cortex, right anterior cingulate cortex, and bilateral superior frontal cortices in MDD (Tadayonnejad et al., 2014). Further, the anterior CC reportedly plays a role in sustaining attention because it contains fibers connecting the bilateral frontal cortices (Rueckert and Levy 1996). A recent review of functional MRI studies reported an association between performance of symbol coding and increased brain activity in the frontal and parietal regions (Forn et al., 2009). The results of the current study corroborated with these previous findings, suggesting that WM microstructural abnormalities are associated with impaired working memory and attention in patients with MDD.

There are some limitations of this study that must be noted. First, all patients with MDD, except one, were medicated at the time of scanning, which could have influenced FA and cognitive performance. Second, the MDD groups and HC groups were not matched for gender, but these differences did not reach statistical significance and previous DTI studies reported no association between FA of the CC and gender differences (Hasan et al., 2008; Lebel et al., 2010). Further studies using more subjects with controlled confounding factors are needed to elucidate detailed correlations between WM microstructural abnormalities and

clinical characteristics of patients with MDD.

In summary, the MDD group showed widespread WM microstructural abnormalities that were correlated with cognitive impairment. The results presented in the study contribute to the understanding of WM pathophysiology in MDD.

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Contributors

Authors Yamada, Takahashi, Ukai and Shinosaki designed the study. Authors Yamada and Takahashi oversaw subject recruitment. Authors Yamada, Ishida, Tsuda and Ohoshi conducted tract-based spatial statistics and the statistical analysis. Author Terada made substantial contributions to the acquisition and processing of the imaging data. Authors Takahashi, Ukai, Tsuji and Shinosaki provided feedback about the study design during the study implementation. Author Yamada wrote the first draft of the manuscript. Author Takahashi, Ishida and Shinosaki contributed to manuscript writing. All authors have approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest related to the study.

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Figure legends

Figure 1. Fractional anisotropy (FA) of major depressive disorder (MDD) and healthy control (HC) groups.

Green indicates mean FA skeleton of all participants. The red voxels indicate regions where the FA of the MDD group was significantly lower, compared with the HC group ($p < 0.05$).

Figure 2. Correlation between fractional anisotropy (FA) and the digit sequencing task and symbol coding.

Green indicates mean FA skeleton of patients with major depressive disorder (MDD). The red voxels indicate a significant positive correlation between FA and the raw score of (a) the digit sequencing task and (b) symbol coding in patients with MDD ($p < 0.05$).

Figure 1

FA of the MDD vs. HC group

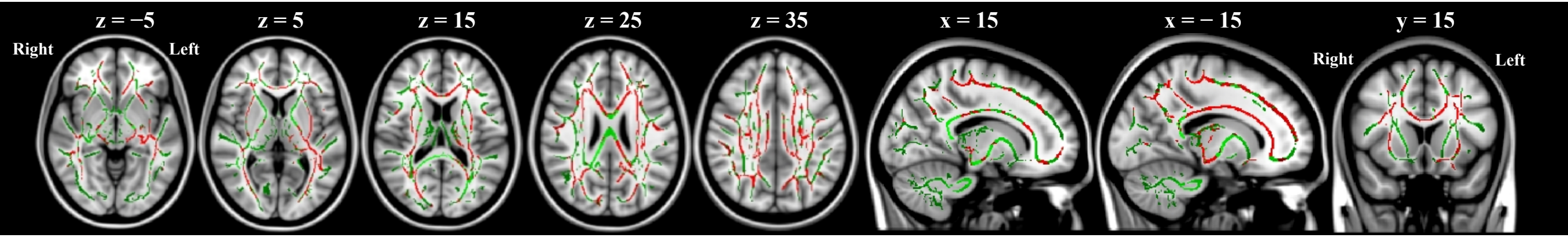
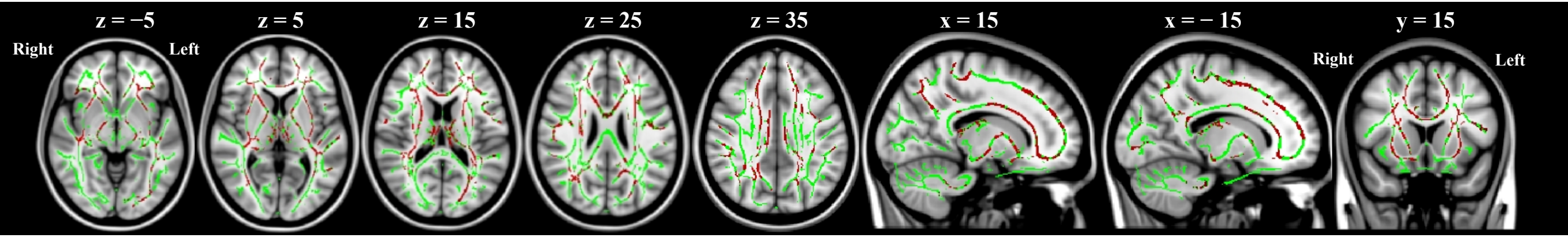


Figure 2

(a) Digit sequencing task



(b) Symbol coding

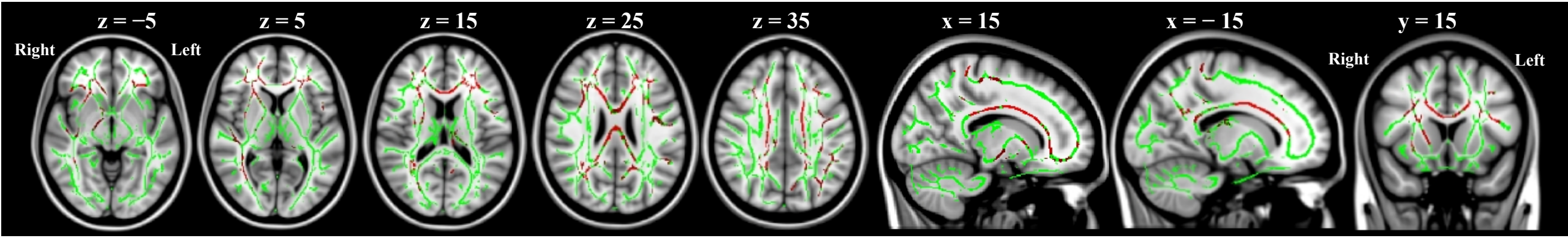


Table 1: Demographic and clinical characteristics

	HC group (n = 21)			MDD group (n = 18)			Statistics	
	Mean	SD	Range	Mean	SD	Range		
Age[a]	41.2	10.0	29–60	45.7	7.68	34–60	F = 1.91	$p = 0.128$
Gender, male/female[b], n	8/13			12/6			$\chi^2 = 2.98$	$p = 0.226$
Duration of illness, years				5.25	7.98			
HAMD				9.77	6.75			
JART[a]	106.2	9.82		103.1	8.81		F = 0.068	$p = 0.306$
Lithium, n				3				
Antidepressant, n				17				
Anticonvulsant, n				1				
Antipsychotic, n				3				
Digit sequencing task[a]	21.3	2.97		17.6	3.91		F = 0.512	$p = 0.002$* (HC > MDD)
Symbol coding[a]	71.4	7.68		55.8	11.7		F = 1.71	$p < 0.000$* (HC > MDD)
List learning[a]	46.0	9.05		36.2	8.89		F = 0.153	$p = 0.002$* (HC > MDD)
Tower of London[a]	18.0	2.03		17.2	2.41		F = 0.367	$p = 0.254$

Significant differences between the two groups are marked. Values marked with * is significant at $p < 0.01$.
[a] Independent samples *t*-test.
[b] χ^2 test.
HC, healthy controls; MDD, major depressive disorder; n, number; SD, standard deviation; HAMD, 17-item Hamilton Rating Scale for Depression; JART, Japanese Adult Reading Test.

Highlights:

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