

# COMT Val158Met, but not BDNF Val66Met, is associated with white matter abnormalities of the temporal lobe in patients with first-episode, treatment-naïve major depressive disorder: a diffusion tensor imaging study

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**Abstract:** We investigated the association between the Val158Met polymorphism of the catechol-O-methyltransferase (*COMT*) gene, the Val66Met polymorphism of the brain-derived neurotrophic factor (*BDNF*) gene, and white matter changes in patients with major depressive disorder (MDD) and healthy subjects using diffusion tensor imaging (DTI). We studied 30 patients with MDD (17 males and 13 females, with mean age  $\pm$  standard deviation [SD] =44 $\pm$ 12 years) and 30 sex- and age-matched healthy controls (17 males and 13 females, aged 44 $\pm$ 13 years). Using DTI analysis with a tract-based spatial statistics (TBSS) approach, we investigated the differences in fractional anisotropy, radial diffusivity, and axial diffusivity distribution among the three groups (patients with the *COMT* gene Val158Met, those with the *BDNF* gene Val66Met, and the healthy subjects). In a voxel-wise-based group comparison, we found significant decreases in fractional anisotropy and axial diffusivity within the temporal lobe white matter in the Met-carriers with MDD compared with the controls ( $P < 0.05$ ). No correlations in fractional anisotropy, axial diffusivity, or radial diffusivity were observed between the MDD patients and the controls, either among those with the *BDNF* Val/Val genotype or among the *BDNF* Met-carriers. These results suggest an association between the *COMT* gene Val158Met and the white matter abnormalities found in the temporal lobe of patients with MDD.

**Keywords:** catechol-O-methyltransferase, brain-derived neurotrophic factor, 3-methoxy-4-hydroxyphenylglycol, homovanillic acid

## Introduction

Catecholamines play an important role in the pathogenesis of major depressive disorder (MDD).<sup>1</sup> Catechol-O-methyltransferase (*COMT*) is a methylation enzyme that plays a role in the degradation of noradrenaline and dopamine, by catalyzing the transfer of a methyl group from S-adenosylmethionine. Biochemical research has established that the enzyme activities in patients with MDD differ from those of nondepressed subjects.<sup>2</sup> The *COMT* gene is located at 22q 11.21. In a multicenter European study, an association was found between the *COMT* gene Val158Met (G324A) functional polymorphism and MDD.<sup>3</sup> The Val allele has been reported to result in three- to fourfold higher activity than the Met allele.<sup>4</sup> One report suggests that there is an association between higher activity of the *COMT* gene Val158Val-type and a poor antidepressant

treatment response.<sup>5</sup> The Met-variants of *COMT* gene Val158Met were shown to be risk variants for depressed mood and low motivation in depressive Swedish men.<sup>6</sup>

Brain-derived neurotrophic factor (BDNF) is a molecular substrate of stress; data have demonstrated that BDNF expression is reduced by stress (an important risk factor for MDD and posttraumatic stress disorder)<sup>7</sup> and correlates to hippocampus volume in patients.<sup>8</sup> The levels of BDNF and its receptor, tropomyosin-related kinase B (TrkB) receptor, are decreased in regions of the hippocampus in postmortem tissue taken from suicide victims and patients with MDD, and in the serum of MDD patients.<sup>9–11</sup> Researchers have investigated the *BDNF* gene for a single nucleotide polymorphism (SNP) that might be linked to MDD. The most common *BDNF* SNP in humans is at codon 66, resulting in the Val66Met protein variant, which prevents the activity-dependent release of BDNF.<sup>12</sup> Men homozygous for the mutation might be at greater risk for MDD.<sup>13</sup> It has been hypothesized that monoamine and BDNF are associated with the pathogenesis of MDD.<sup>14</sup>

The white matter (WM) abnormalities constitute one element of the pathogenesis of MDD.<sup>15–17</sup> Various fiber tract alterations have been seen in MDD patients.<sup>18–22</sup> Magnetic resonance imaging (MRI) is a noninvasive method used to examine WM abnormalities. Diffusion tensor imaging (DTI) is an MRI technique that can study the orientation and integrity of WM fiber tracts in vivo.<sup>23</sup> DTI-based quantitative measures, such as fractional anisotropy (FA), represents intact myelin and axons, and has been shown to be a useful marker of the microstructural changes in WM.

Although several studies using a voxel-based DTI analysis demonstrated lower FA values in the frontal, temporal, and parietal lobes and the cerebellum of MDD patients,<sup>24–28</sup> such an analysis is not a mainstream of statistical parametric mapping and is not officially supported. Therefore, there has not been a consensus about the optimal method to spatially normalize FA images and the size of the smoothing kernel. A voxel-wise approach of tract-based spatial statistics (TBSS) has been introduced. The TBSS method projects all subjects' FA data onto an average FA tract skeleton before applying voxel-wise cross-subject statistics, and it minimizes the misalignment effects and is more robust and sensitive than voxel-based DTI analyses.<sup>18</sup>

The findings from individual reports of WM abnormalities in MDD patients indicate a widespread pattern of alterations, and the extent of WM abnormalities might be associated with clinical features. Indeed, the severity of illness and poorer treatment outcomes have been associated with increased

WM pathology, indicating that patients with a greater illness burden are more likely to have microstructural damages.<sup>29</sup> The most pronounced WM FA reductions have been observed in the main body and genu of the corpus callosum, consistent with some, but not all, DTI reports in MDD. FA values of the WM in the right frontal lobe, right fusiform gyrus, left frontal lobe, and right occipital lobe were also demonstrated to be reduced. Fiber tracking has shown that the main fascicles involved were the right inferior longitudinal fasciculus, right inferior fronto-occipital fasciculus, right posterior thalamic radiation, and interhemispheric fibers running through the genu and body of the corpus callosum.<sup>30</sup>

Carballedo et al<sup>31</sup> recently reported that they observed a significant interaction, in the uncinated fasciculus, between a *BDNF* allele and diagnosis: patients carrying the *BDNF* Met allele had lower FA values in the uncinated fasciculus compared with healthy subjects carrying the Met allele. Kim et al<sup>32</sup> reported an association between altered WM connectivity and *COMT* gene Val158Met polymorphism in panic disorder patients. We hypothesize that the *COMT* gene and the *BDNF* gene are associated with WM connectivity in MDD patients.

In the present study, therefore, we compared the status of polymorphism of the *COMT* gene or *BDNF* gene and DTI findings between drug-naïve MDD patients and age- and sex-matched healthy controls.

## Subjects and methods

### Subjects

Thirty first-episode, right-handed, treatment-naïve outpatients were recruited. Major depressive episodes were diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) according to the DSM-IV, text revision (TR) criteria. The severity of depression was evaluated using the 17-item Hamilton Rating Scale for Depression (HAM-D17). Only those patients with a HAM-D17 score  $\geq 14$  were eligible for the study. Exclusion criteria were: any history of neurological disease or other physical disease, and comorbidity with other mental disorders (no evidence of schizoaffective disorder, bipolar disorder, Axis II personality disorders, or mental retardation). In all, 17 subjects were male, and 13 were female. The age range was from 20 to 67 years, with a mean  $\pm$  standard deviation (SD) age of  $44 \pm 12$  years. Similarly, 30 right-handed healthy subjects, 17 male and 13 female, with mean age  $44 \pm 13$  years were recruited from the community.

The DTI scans for all 60 subjects were performed on the day when each subject was enrolled. The 30 control subjects

were interviewed by the same psychiatrists that interviewed the MDD patients, using the Structured Clinical Interview for DSM-IV, nonpatient edition. None of the control subjects had a history of serious medical or neuropsychiatric illness or a family history of major psychiatric or neurological illness in their first-degree relatives, and all were well matched with the patients in terms of age, sex, and years of education. All subjects were given complete information about the procedures. Written informed consent was obtained from all subjects via forms approved by the local Ethics Committee of the University of Occupational and Environmental Health, Kitakyushu, Japan.

## Methods

### Diffusion tensor images: MRI scanning protocol

All MRI examinations were performed using a 3T MRI system (Signa® EXCITE™ 3T; GE Healthcare, Little Chalfont, UK) with an eight-channel brain phased-array coil. DTIs were acquired by a single-shot, spin-echo planar sequence, with the following parameters: TR/TE = 12,000/83.3 msec; 4 mm slice thickness; no gap; field of view = 26 cm; number of excitations = 1, spatial resolution = 1.02 × 1.02 × 4 mm. Diffusion gradients (b-value of 1,000 sec/mm<sup>2</sup>) were always applied on two axes simultaneously around the 180-degree pulse. The diffusion properties were measured along 25 noncollinear directions. The spatial distortion of diffusion-weighted MRIs was corrected based on each T2-weighted echo-echo planar image (b=0 sec/mm<sup>2</sup>)<sup>33</sup> using registration functional MRI of the brain (FMRIB) tools.

### Image processing

Maps of FA were computed for all subjects from the DTIs, after eddy current correction and automatic brain extraction using the FMRIB Diffusion Toolbox, which is part of the FMRIB Software Library (The Oxford Centre for Functional MRI of the Brain, Oxford, UK).<sup>34</sup> We performed a voxel-wise statistical analysis of the DTI data using TBSS<sup>35</sup> (implemented in the FMRIB Software Library 4.1.6). The FA, radial diffusivity (RD), and axial diffusivity (AD) were created by fitting a tensor model to the raw diffusion data. Brain extraction was then performed using the Brain Extraction Tool 2.1.<sup>36</sup>

The FA data of all subjects were aligned into a common space by means of nonlinear registration.<sup>37</sup> Next, a mean FA image was created and thinned to create a mean FA skeleton representing the centers of all tracts common to the group. This skeleton was thresholded at FA > 0.2. Each subject's aligned FA data were then projected onto this skeleton, and

the resulting data were fed into a voxel-wise cross-subject statistical analysis. Subsequently, other relevant DTI output images (AD and RD) were projected onto the mean FA skeleton so that other diffusivity values could be compared between groups in the same spatial location.

We compared the DTI metrics between the MDD and control groups using a TBSS analysis.

### Genotyping and serum catecholamine metabolites assay

Genomic DNA was extracted from peripheral leukocytes using a QIAamp® DNA Blood Kit (Qiagen, Venlo, the Netherlands) and was stored at -20°C until used for analysis. Genotyping for the presence of the *BDNF* Val66Met and *COMT* Val158Met polymorphisms was performed using direct sequencing in the region.

We analyzed the subjects' plasma concentrations of homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) by high-performance liquid chromatography with electrochemical detection (HPLC-ECD). The plasma HVA levels were analyzed by HPLC-ECD according to the method of Yeung et al,<sup>38</sup> with slight modification. In brief, each cyanobonded solid-phase extraction cartridge was preconditioned with methanol, followed by glass-distilled water. To each cartridge we added 0.3 mL of plasma sample or standard, and 0.1 mL of working internal standard solution (5 ng of 5-hydroxyindolecarboxylic acid in 0.01 M KH<sub>2</sub>PO<sub>4</sub>, pH 7.2). The samples were deproteinized with 1 mL of acetonitrile. After mixing by vortex and centrifugation (1,760 × g, 4°C for 10 minutes), an aliquot (5 µL) of supernatant was allowed to pass through the cartridge slowly, under a mild vacuum (15 mmHg). The cartridge was washed with 0.2 mL of distilled water and extracted containing 1 mL of ethylacetate, and then an aliquot was evaporated to dryness under nitrogen gas. After dissolution in mobile phase (200 µL), a 10 µL portion of this solution was injected into the HPLC system. The detection limit was 0.5 ng/mL, and the calibration curve was linear up to 40 ng/mL. The intra- and interassay coefficients of variation were 6% and 8%, respectively. The recovery rate was more than 80%.

The subjects' plasma MHPG levels were also analyzed by HPLC-ECD, according to the method of Minegishi and Ishizaki.<sup>39</sup> In brief, the plasma was separated by centrifugation at 600 × g at 4°C. Extraction was performed under a vacuum using Bond-Elut columns (Varian Medical Systems, Inc., Palo Alto, CA, USA) prepacked with 100 mg of C18-bonded silica (40 µm) in a 1 mL capacity disposable syringe. The columns, which were inserted into a vacuum chamber connected to an

aspirator, were prepared by washing with 1 mL methanol followed by 1 mL of water. After the addition of 50  $\mu$ L of a solution of vanillyl alcohol (internal standard equivalent to 5 ng/mL) to 1 mL of plasma, the samples were passed through the columns, followed by 0.75 mL of water to rinse off both residual samples and easily eluted hydrophilic compounds.

The adsorbed materials were eluted with 200  $\mu$ L of methanol to a 0.1 M phosphate buffer (pH 4.8) mixture (40:60, v/v [volume/volume]). A 20  $\mu$ L portion of this solution was injected into the HPLC system. The detection limit was 0.5 ng/mL, and the calibration curve was linear up to 40 ng/mL. The intra- and interassay coefficients of variation were 6% and 8%, respectively. The recovery rate was more than 80%.

### Statistical analyses

The significance threshold for between-group differences was set at family-wise error (FWE)-corrected  $P < 0.05$ ; this was corrected for multiple comparisons across voxels by using the threshold-free cluster-enhancement option. The number of permutations was set to 20,000 in all voxel-wise analyses. The chi-square test was used to compare the number of patients with the *COMT* or *BDNF* genotype Val/Val, and the number of Met-carriers in both the MDD patient and the control groups. The unpaired *t*-test was used to compare the items of the HAMD17 scores, and the plasma levels of MHPG and HVA between the Val/Val group and Met-carriers in the MDD patient group. The unpaired *t*-test was also used to compare serum BDNF levels between the MDD patients and the healthy controls. A significance level of  $P < 0.05$  was used. Statistical procedures were performed using the Japanese version of SPSS, version 15 (SPSS Inc., Chicago, IL, USA).

## Results

The genotype distributions of the *COMT* Val158Met polymorphism were determined in both the MDD patients and the control subjects, as shown in Table 1. The table provides the allele and genotype distributions as well as the chi-square and *P*-values of Hardy–Weinberg equilibria. As can be seen in Table 2, there were no significant differences among the MDD patients in each item of the HAMD17, with the exception that the responses to item 16 (weight loss) differed significantly between the *COMT* Val/Val group and the *COMT* Met-carriers.

The analysis of the plasma levels of catecholamine metabolites (MHPG and HVA) revealed no significant differences between the MDD patients and the controls (MHPG was  $5.3 \pm 1.0$  ng/mL for MDD and was  $5.4 \pm 1.2$  ng/mL for controls [ $P = 0.23$ ]; HVA was  $5.5 \pm 1.4$  ng/mL for MDD

**Table 1** Gene distribution of *COMT* and *BDNF* in patients with MDD and healthy controls

	Control	$\chi^2$	<i>P</i> -value	Number of patients	$\chi^2$	<i>P</i> -value
<b><i>COMT</i> Val158Met</b>						
GG	10			9		
GA	18	2.566	0.1099	16	0.222	0.5377
AA	2			5		
<b><i>BDNF</i> Val66Met</b>						
GG	18			15		
GA	10	0.14	0.7082	8	1.12	0.2900
AA	2			7		

**Abbreviations:** *BDNF*, brain-derived neurotrophic factor; *COMT*, catechol-O-methyltransferase.

and was  $5.1 \pm 0.8$  ng/mL for the controls [ $P = 0.13$ ]). In addition, no significant differences between the Val/Val group and the Met-carriers were found in plasma MHPG, a major metabolite of norepinephrine ( $5.0 \pm 1.4$  ng/mL [Val/Val group];  $4.9 \pm 1.5$  [Met-carriers] [ $P = 0.85$ ]) or in plasma HVA, a major metabolite of dopamine ( $8.5 \pm 2.7$  ng/mL [Val/Val group];  $8.7 \pm 2.7$  ng/mL [Met-carriers] [ $P = 0.81$ ]). The serum BDNF levels were significantly lower in the MDD patients ( $4.8 \pm 0.4$  ng/mL) compared with the controls ( $5.6 \pm 0.5$  ng/mL) ( $P = 0.044$ ).

**Table 2** Between-group comparisons of scores on each item of the HAMD17, in MDD patients with the *BDNF* gene polymorphism

HAMD 17-item	Val/Val	Met-carrier	<i>P</i> -value
1	2.53 $\pm$ 0.96	2.60 $\pm$ 0.88	0.84
2	0.8 $\pm$ 0.75	0.87 $\pm$ 0.72	0.81
3	1.40 $\pm$ 0.80	1.93 $\pm$ 1.18	0.17
4	1.33 $\pm$ 0.60	1.07 $\pm$ 0.57	0.23
5	1.07 $\pm$ 0.25	0.93 $\pm$ 0.44	0.33
6	1.13 $\pm$ 0.60	1.20 $\pm$ 0.65	0.76
7	2.80 $\pm$ 0.91	2.93 $\pm$ 0.93	0.7
8	0.87 $\pm$ 0.65	1.00 $\pm$ 0.73	0.6
9	0.80 $\pm$ 0.65	0.67 $\pm$ 0.70	0.6
10	1.67 $\pm$ 1.14	1.67 $\pm$ 1.01	1
11	1.53 $\pm$ 0.81	1.40 $\pm$ 0.80	0.66
12	1.07 $\pm$ 0.68	1.07 $\pm$ 0.25	1
13	0.8 $\pm$ 0.54	1.00 $\pm$ 0.52	0.32
14	1.07 $\pm$ 0.57	1.47 $\pm$ 0.62	0.08
15	0.73 $\pm$ 0.77	0.60 $\pm$ 0.80	0.65
16	0.53 $\pm$ 0.72	0.80 $\pm$ 0.91	0.039
17	0.20 $\pm$ 0.40	0.47 $\pm$ 0.72	0.23
Total	19.50 $\pm$ 6.35	21.70 $\pm$ 4.91	0.31

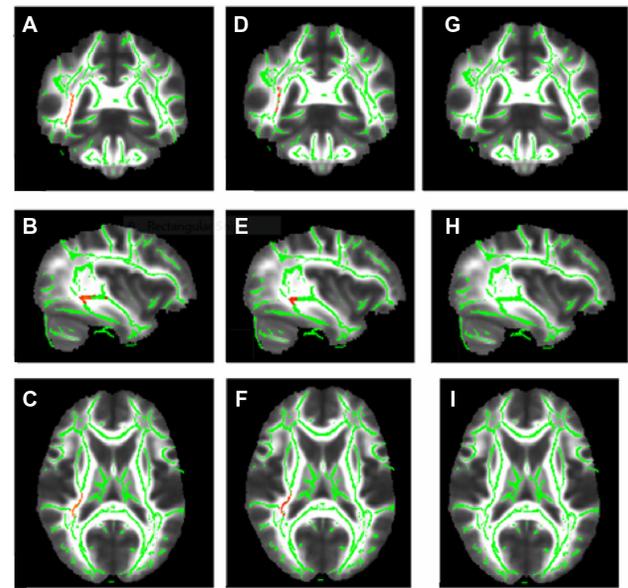
**Notes:** 1, Depressed mood; 2, Feeling of guilt; 3, Suicide; 4, Insomnia early; 5, Insomnia middle; 6, Insomnia late; 7, Work and activity; 8, Retardation; 9, Agitation; 10, Anxiety (psychological); 11, Anxiety (somatic); 12, Somatic symptoms (gastrointestinal); 13, Somatic symptoms (general); 14, Genital symptoms; 15, Hypochondriasis; 16, Loss of weight; 17, Insight.

**Abbreviations:** *BDNF*, brain-derived neurotrophic factor; HAMD17, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder.

Regarding *BDNF* Val66Met, no significant differences between the Val/Val group and the Met-carriers were observed in plasma MHPG ( $5.0 \pm 1.4$  ng/mL [Val/Val group];  $4.9 \pm 1.5$  [Met-carriers] [ $P=0.85$ ]), plasma HVA ( $5.3 \pm 1.1$  ng/mL [Val/Val group];  $5.0 \pm 1.3$  [Met-carriers] [ $P=0.54$ ]), or serum BDNF ( $5.4 \pm 1.2$  ng/mL [Val/Val group];  $4.8 \pm 1.6$  [Met-carriers] [ $P=0.39$ ]). No differences were observed in any items of the HAMD17 between the Val/Val genotype and the Met-carriers (Table 3).

In the voxel-wise-based group comparison, no significant differences were observed regarding FA, AD, or RD, in all patients compared with the controls. We found a significant FA decrease ( $P < 0.05$ ) within the temporal lobe WM in the Met-carriers among the MDD patients compared with those of the healthy controls (Figure 1A–C), on the basis of the Johns Hopkins University (JHU) white-matter tractography atlas and the International Consortium for Brain Mapping DTI-81 WM labels (part of the FMRIB Software Library package). In the voxel-wise-based group comparison, there was no significant difference in FA, AD, or RD, between the MDD patients and the healthy controls.

After dividing the MDD patients into genotype subgroups, we found a significant FA decrease ( $P < 0.05$ ) in the temporal lobe among the MDD patients who were Met-carriers



**Figure 1** Corrected *P*-maps for the *COMT* gene polymorphism.

**Notes:** These maps show the regions where FA is reduced in the red voxels (A–C), where AD is reduced in the red voxels (D–F), and where RD shows no change (G–I). The FA, AD, and RD skeletons are projected in green on the MNI 152 template (Montreal Neurological Institute, Montreal, QC, Canada) average brain section.

**Abbreviations:** AD, axial diffusivity; *COMT*, catechol-*O*-methyltransferase; FA, fractional anisotropy; RD, radial diffusivity.

**Table 3** Between-group comparisons of scores on each item of the HAMD17 for the two groups of patients with MDD

HAMD 17-item	Val/Val	Met-carrier	P-value
1	2.11±0.34	2.32±0.64	0.71
2	0.73±0.75	0.80±0.69	0.65
3	1.67±0.59	1.81±1.03	0.19
4	1.48±0.76	1.29±0.49	0.18
5	1.02±0.29	1.09±0.38	0.30
6	1.13±0.60	1.20±0.65	0.76
7	2.49±0.67	2.99±1.08	0.52
8	0.91±0.72	1.14±0.81	0.53
9	0.92±0.54	0.71±0.52	0.49
10	1.82±1.02	1.52±0.94	0.78
11	1.23±0.74	1.57±0.79	0.72
12	0.98±0.68	1.12±0.43	0.92
13	0.87±0.63	1.14±0.61	0.43
14	1.21±0.62	1.44±0.78	0.11
15	0.65±0.52	0.63±0.79	0.59
16	0.53±0.69	0.78±0.88	0.13
17	0.37±0.41	0.52±0.51	0.49
Total	20.33±7.29	20.97±5.84	0.51

**Notes:** 1, Depressed mood; 2, Feeling of guilt; 3, Suicide; 4, Insomnia early; 5, Insomnia middle; 6, Insomnia late; 7, Work and activity; 8, Retardation; 9, Agitation; 10, Anxiety (psychological); 11, Anxiety (somatic); 12, Somatic symptoms (gastrointestinal); 13, Somatic symptoms (general); 14, Genital symptoms; 15, Hypochondriasis; 16, Loss of weight; 17, Insight.

**Abbreviations:** HAMD17, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder.

compared with the corresponding values among the healthy controls (Figure 1A–C). Significantly decreased AD in the temporal lobe ( $P < 0.05$ ) was also found in the Met-carrier MDD patients compared with the healthy controls (Figure 1D–F). Significantly decreased AD in the temporal lobe ( $P < 0.05$ ) was also found in the MDD patients compared with the controls (Figure 1D–F). Moreover, the genotype–diagnostic interaction effect on FA was seen in the same position (uncorrected  $P < 0.05$ ), although no voxels could survive after the correction for multiple comparisons (FWE  $< 0.05$ ). The results of the image analyses are shown in Table 4.

No significant differences were observed in FA or AD, at any brain regions, between the MDD patients with the *COMT*

**Table 4** The results of image analyses

Anatomical regions	Cluster size	P-value (FWE-corrected)	MNI coordinate		
			x	y	z
<b>FA analysis (HS &gt; MDD in Met carriers)</b>					
Right temporal lobe	81	0.046	54	87	84
	10	0.049	53	91	80
<b>AD analysis (HS &gt; MDD in Met carriers)</b>					
Right temporal lobe	151	0.046	58	90	87
	9	0.049	51	81	71

**Abbreviations:** AD, axial diffusivity; FA, fractional anisotropy; FWE, family-wise error; HS, healthy subjects; MD, mean diffusivity; MDD, major depressive disorder; MNI, Montreal Neurological Institute.

Val/Val genotype and the healthy controls with the *COMT* Val/Val genotype. No significant difference was observed in RD between the MDD patients and the healthy controls, both among the *COMT* Val/Val group and the *COMT* Met-carriers (Figure 1G–I). In addition, there were no significant differences regarding FA, AD, or RD between the Val/Val group and the Met-carriers among the MDD patients, and no correlations in FA, AD, or RD were observed, at any regions of the brain, between the MDD patients and the healthy controls, both those with the *BDNF* Val/Val genotype and the *BDNF* Met-carriers (Table 4).

## Discussion

In the genotype comparison (significant genotype–diagnosis interactions), we found that the reduction of the FA values in the temporal lobe was significantly larger in the MDD patients compared with the healthy subjects. FA has been shown to have an increased sensitivity to WM damage, as its decrease has been reported in the normal-appearing WM of patients with MDD.<sup>24</sup> The use of other DTI parameters, such as AD, which is related to axonal loss, and RD, which is associated with demyelination,<sup>37,40</sup> may increase the specificity of DTI to particular microstructural abnormalities. The most noteworthy finding in the present study was that the FA and AD, but not the RD, in the temporal lobe in the Met-carriers with MDD were significantly decreased compared with those in the healthy controls. These results may indicate that neuronal degeneration (axonal loss) can occur in the temporal lobe of Met-carriers with MDD.

In contrast, Seok et al<sup>41</sup> recently reported that FA reduction in the temporal lobe was significant only in the MDD patients with the Val/Val group of *COMT* Val158Met polymorphism. This finding indicates that MDD patients with a homozygote Val gene might have further abnormalities and brain pathological changes. Taken together, the above-described findings show that it is controversial whether the *COMT* Val158Met polymorphism is associated with structural changes of WM in the temporal lobe.

However, no significant differences were found in the plasma levels of MHPG and HVA between the present MDD patients and the control subjects. Depression is a heterogeneous condition characterized by multiple symptoms and subtypes. The different symptoms and subtypes are likely mediated by different neurocircuitry, and neurotransmitters such as noradrenaline, dopamine, and serotonin, and they might or might not be present in any particular individual with MDD. MDD might be characterized by an increase or a decrease in certain symptoms.

We reported that MDD patients with high plasma MHPG demonstrated severe anxiety and agitation, whereas those with low MHPG and/or HVA demonstrated severe psychomotor retardation.<sup>42,43</sup> We suspect that this is one of the reasons that no significant between-group differences were found in the catecholamine metabolites, in the present study.

In addition, each component of depressive symptoms might be related to the some brain regions and neurocircuits. Anhedonia, for example, has been found to be positively correlated with the ventromedial prefrontal cortex activity and negatively correlated with amygdala/ventral striatal activity in response to “happy” stimuli, using functional MRI (fMRI).<sup>44</sup> Psychomotor symptoms have been associated with frontal and caudate abnormalities in depression.<sup>45</sup> A recent fMRI study has shown that vulnerability to MDD is associated with temporofrontolimbic decoupling that is selective for self-blaming feelings.<sup>46</sup>

According to the meta-analysis of Liao et al<sup>30</sup> using DTI, there are four consistent locations of decreased FA in patients with MDD: WM in the right frontal lobe, the right fusiform gyrus, the left frontal lobe, and the occipital lobe. Fiber tracking showed that the main fascicles involved were the right inferior fronto-occipital fasciculus, the right posterior thalamic radiation, and interhemispheric fibers running through the genu and the body of the corpus callosum.

Taken together, these results indicate that *COMT* gene Val158Met polymorphism did not reflect the plasma and cerebrospinal fluid levels of catecholamine metabolites. The weight loss item scores of the HAM-D17 were significantly lower in the present *COMT* Val/Val group than in the Met-carriers. It might be possible that the higher activity of COMT leads to reduced physical activity by influencing the catecholaminergic pathways.

The specificity of WM hyperintensities to age-associated vascular depression<sup>47</sup> reinforces the notion that MDD is a heterogeneous disorder. Although the data suggest that T2-weighted WM is related to late-onset MDD, findings suggestive of microstructural WM changes, as evinced by DTI, in young adults with MDD were reported by Li et al.<sup>48</sup> The age-associated relationship between WM and MDD may preclude the use of this trait to identify young individuals at risk of developing MDD. Nevertheless, an understanding of the mechanisms by which microvascular lesions lead to depression may help elucidate important pathophysiological pathways and facilitate the development of new treatments. In the present study, however, no correlations were found with the *BDNF* Val/Met polymorphism in patients with MDD.

On the other hand, Carballo et al<sup>31</sup> reported that they observed a significant interaction between *BDNF*

alleles in the uncinate fasciculus and diagnosis. In short, their patients with the *BDNF* Met allele had smaller FA in the uncinate fasciculus compared with the patients in the Val/Val group and compared with healthy controls with Met allele. In the present study, we did not examine the regions of the temporal lobe in detail. One of the reasons for the discrepancy between the results of Carballido et al<sup>31</sup> and those of the present study was that our MDD patients were at the early stage of depressive state and were drug-naïve.

Our finding that the serum BDNF levels in the MDD patients were lower than those in the healthy controls is in agreement with previous reports.<sup>11,49–51</sup> We also found that the *BDNF* gene Val66Met polymorphism was not associated with serum BDNF levels in patients with MDD and that the *BDNF* Val66Met polymorphism is independent of the WM disturbance in MDD. Taken together, these results indicate that the *BDNF* gene Val66Met polymorphism is not critical for WM disturbances in patients with MDD.

The present study has several limitations. The sample size was too small to allow a second statistical analysis. The sample was heterogeneous, and the severity of illness was relatively moderate. A replication study that accounts for these limitations should be performed to confirm our preliminary results. Since the *COMT* gene Met-carriers showed more decreased body weight (Table 2), the possibility that the finding reflected the changed distribution in the brain could not be completely ruled out.

In conclusion, we observed an association between the *COMT* gene Val158Met polymorphism and the reduction of FA and AD, but not RD, in the temporal lobe of patients with MDD.

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## Disclosure

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