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Tryptophan hydroxylase-2 polymorphism is associated with white matter integrity in first-episode, medication-naïve major depressive disorder patients

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ABSTRACT

Considerable evidence suggests that the tryptophan hydroxylase-2 (TPH2) gene is associated with the pathophysiology of major depressive disorder (MDD). In the present study, we investigated alterations of white matter (WM) integrity and the impact of TPH2 polymorphism on WM in a sample of 118 first-episode, medication-naïve, MDD patients and 118 well-matched healthy controls. Whole brain analyses of fractional anisotropy (FA) were performed using tract-based spatial statistics (TBSS). The results showed that the MDD group had significantly reduced FA values for the genu and body of the corpus callosum (CC) and the bilateral anterior corona radiate (ACR). In the MDD patient group, the GG homozygote subgroup exhibited a widespread reduction of FA (uncorrected) and significantly reduced FA in the left retrolenticular portion of the internal capsule and left superior longitudinal fasciculus (SLF) compared with those of the T carriers (GT/TT) (FWE corrected). No significant correlation was found between the FA values in any brain region and the patients' clinical variables. Our findings demonstrate the presence of abnormal white matter integrity in untreated patients with first-episode depression. TPH2-rs4570625 polymorphisms may be involved in the pathological mechanism of WM microarchitecture in patients.

1. Introduction

Although the etiology of major depressive disorder (MDD) has not been well recognized, growing evidence suggests that the pathophysiology is multifaceted and may involve multiple complex interactions between genetic and environmental factors that produce changes in the structure and function of neural networks associated with emotional processing (Kupfer et al., 2012). Diffusion tensor imaging (DTI) is a non-invasive assessment of brain white matter integrity that examines water diffusivity in the brain. Fractional anisotropy (FA) is a commonly used metric to provide information about the relative axon size, myelination, axon connections, and orientation. Reduced FA values have been exhibited in regions with reduced white matter structural integrity and axon connectivity. Numerous studies on MDD conducted using DTI have confirmed white matter abnormalities in tracts and regions associated with mood regulation, which include the superior longitudinal fasciculus (SLF) (Jiang et al., 2017; Murphy and Frodl, 2011), internal capsule (Chen et al., 2016; Guo et al., 2012; Tatham et al., 2016), external capsule (Guo et al., 2012), corpus callosum (CC) (Chen et al., 2016; Choi et al., 2015; Guo et al., 2012; Jiang et al., 2017; Won et al., 2016), uncinate fasciculus (Lewinn et al., 2014), and corona radiate (Choi et al., 2015; Guo et al., 2012).

MDD pathology is related to dysfunction of the monoaminergic system. Many monoaminergic genes, including the tryptophan hydroxylase-2 (TPH-2) gene, have been repeatedly studied (Won and Ham, 2016). The TPH-2 gene is considered to be a promising candidate gene associated with depression. As the rate-limiting enzyme in the synthetic brain serotonin pathway, TPH-2 may play an important role in maintaining the normal serotonin level of the central nervous system (Chen et al., 2016; Zhang et al., 2004). Numerous candidate TPH-2 variants have been prominently associated with MDD. TPH-2 gene polymorphisms, namely rs4570625 (Gao et al., 2012; Wigner et al.,

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2018), have demonstrated strong epidemiological associations with MDD. TPH-2 variations involved in TPH-2 gene expression can alter the physiological processes of 5-HT and cause an imbalance in the 5-HT levels. Changes in the 5-HT level have been noted to affect axons and dendrite growth (Trakhtenberg and Goldberg, 2012). Additionally, transgenic knockout of TPH2 in mice has been shown to lead to global wiring abnormalities in serotonergic neurons (Mosienko et al., 2015). Therefore, TPH-2 polymorphisms may plausibly affect axonal growth and even white matter integrity during development. An increasing number of genetic-neuroimaging studies have reported significant evidence that genetic variation in 5-HT-related genes, including the TPH2 gene, has an effect on brain structure and morphology (Won and Ham, 2016; Zhang et al., 2018). Among numerous genetic-neuroimaging studies, recent research has further confirmed that the TPH2-rs4570625 polymorphism is associated with human brain structure. Han et al. found significant genotype-by-diagnosis interactions between TPH2-rs4570625 and a diagnosis of MDD for the local gyrification index (LGI) in the right rostral anterior cingulate cortex (rACC). Compared with that of the healthy controls in the G-homozygote group, the LGI values of the right rACC were significantly increased in G-homozygote MDD patients, but no significant difference was found in the LGI values of the right rACC between the MDD patients and healthy controls in the T-allele carrier subgroup (Han et al., 2017). Another study showed that the mean connectivity in the rich club was larger in G/T and T/T carriers than in TPH2-rs4570625 G/G carriers in healthy Caucasian participants (Markett et al., 2017). Thus, the TPH-2 gene, which affects serotonin neurotransmission in the brain, may be associated with changes in white matter integrity in MDD patients.

In the present study, first we aimed to investigate altered white matter integrity in first-episode, medication-free, MDD patients. Then, we attempted to explore the associations of the rs4570625 polymorphism of the TPH2 gene with the white matter microarchitecture in MDD patients.

2. Methods

2.1. Participants

We recruited 118 first-episode, medication-naive, MDD patients and 118 well-matched healthy controls. All participants in this study were right-handed and were18–60 years old. The severity of depression and anxiety was assessed by an experienced psychiatrist using the 17-item Hamilton Depression Rating Scale (HDRS, Hamilton 1960) and the 14-item Hamilton Anxiety Scale (HAMA), respectively. Depressed individuals were recruited from the outpatient clinic or inpatient wards of the Department of Psychiatry, the First Affiliated Hospital of Kunming Medical University. Two experienced psychiatrists independently established the MDD diagnosis according to the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 2000). All patients had a total score of 17 or greater on the HDRS-17. Data on age, sex and years of education were collected. The exclusion criteria included the following items: (1) another diagnosed axis I psychiatric disorder; (2) a history of neurological illnesses or other severe diseases; (3) a history of brain injury or obvious psychiatric symptoms; (4) substance abuse; (5) pregnant or nursing women and (6) an inability to undergo an MRI scan, including subjects with mental limitations.

According to the same exclusion criteria used for the MDD patients, a total of 118 healthy subjects well-matched with the MDD patients in terms of age and gender were recruited from the local community via advertisements.

Our research was approved by the Institutional Review Board of Kunming Medical University, Yunnan Province, P. R. China (ClinicalTrials.gov, NCT00703742).

2.2. Genotyping

Genomic DNA was extracted from the peripheral venous blood of all participants. Genotyping of the TPH2 rs4570625 polymorphism was performed using the matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) Mass-ARRAY method as described previously (Gu et al., 2017; Jian et al., 2016; Xu et al., 2017) by the Beijing Huada Genome Company.

2.3. Image acquisition

MRI scans were performed by a skilled radiological technician on a Philips Achieva 3.0-T MRI scanner. Restraining foam pads were used to minimize head motion. All subjects underwent volumetric T1 and T2 examinations to exclude obvious structural abnormalities, and then diffusion tensor images were acquired parallel to the anterior-posterior commissure line using a single-shot echo planar imaging sequence. The scan parameters were as follows: repetition time (TR)/echo time (TE) = 6800 ms/80 ms; matrix size = 116 × 112; voxel size = 1.98 mm × 2.05 mm × 3 mm; slice thickness = 3 mm; no gap; field of view (FOV) = 230 mm × 230 mm; flip angle = 90°; and 50 contiguous axial slices. The diffusion sensitizing gradients were applied along 33 non-collinear directions (b = 1000 s/mm^2) with acquisition without diffusion weighting (b = 0).

2.4. Image data processing

All diffusion tensor images were processed using the Functional MRI of the Brain (FMRIB) software library (FSL version 5.0.8, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/). The voxel-wise statistical analysis was performed using TBSSs (Smith et al., 2006). First, for each subject, the DTI data were corrected for head motion and eddy current distortions using an affine transformation of the b = 0 images. Then, the notif brain mask was obtained from the b0 image using a brain extraction tool (BET). Finally, the diffusion tensor models were fitted at each voxel, and the FA maps were obtained by this step.

After the above steps, FA images from each participant were aligned to the FMRIB58_FA template image and transformed into a 1 × 1 × 1 mm^3 standard space (Montreal Neurological Institute 152 standard) using the FMRIB Non-linear Image Registration Tool (FNIRT). Then, a mean FA skeleton was created using an FA threshold ≥0.2.

2.5. Statistical analysis

Demographic and clinical characteristics were compared between the patients and controls using a two-sample t-test for continuous variables (age, years of education, duration (months), and HDRS and HAMA scores) and a Chi-square test for sex. The same statistical methods were used in different genotype subgroups within the MDD and HC groups.

For imaging data analysis, a voxel-wise statistical analysis was performed using the FSL Randomize program. We performed three comparisons of the FA values: (1) comparison between the two groups; (2) comparison between different genotype subgroups within the MDD group and (3) comparison between different genotype subgroups within the HC group. The age, education level, and gender were included as covariates in all analyses with 5000 permutations, and $p < 0.05$ was considered statistically significant after family-wise error (FWE) correction for multiple comparisons using the threshold-free cluster enhancement (TFCE) option (Smith and Nichols, 2009). The anatomical white matter tracts were identified with the John Hopkins University (JHU) ICBM-DTI-81 white matter labels in FSL. Then, we defined whole white matter tracts that showed significantly different FA values between the group comparisons as the regions-of-interests (ROIs) to confirm the TBSS results. For each ROI, a binary mask was created to extract individual means of the FA values using FSL.

We performed a multivariate analysis of covariance (MANCOVA) with age, sex, and education as covariates to compare the FA values of ROIs between the MDD and HC groups. Pearson's partial correlation analysis was performed to investigate the association between the FA values of the ROIs and clinical variables, such as the HDRS score and illness duration of the MDD patients, after adjusting for age, gender, and education level. The same statistical methods were used to examine the impact of TPH2 rs4570625 and the clinical characteristics on the FA values in significant regions from the TBSS analyses within the MDD group. The statistical analyses were performed using the SPSS 19.0 software.

3. Results

3.1. Demographic and genotypic characteristics

We found no significant differences in age ($t = 1.438$, $p = 0.152$) and gender ($\chi^2 = 0.078$, $p = 0.781$) but did find differences in the education level ($t = -5.02$, $p < 0.0001$), HDRS-17 score ($t = 52.039$, $p < 0.0001$) and HAMA score ($t = 41.92$, $p < 0.0001$) between the MDD and HC groups. The distribution of the three TPH2 genotypes was consistent with the Hardy-Weinberg equilibrium in each group ($p > 0.05$). No significant difference in the TPH2 genotype frequency ($p = 0.315$) and allele frequencies ($p = 0.228$) were observed between the two groups. No significant differences in age, gender, education level, and the HDRS-17 and HAMA scores were found between the GG homozygotes and T-allele carriers within the HC group. Additionally, no significant differences in the age and education level was found between the GG homozygotes and T-allele carriers in the MDD group, but a significant difference was found for gender ($p = 0.016$) (see Table 1).

3.2. Decreased FA in the MDD patients vs. controls

We found significantly reduced FA values in the MDD group in many of the white matter (WM) regions, including the genu and body of the CC, bilateral anterior corona radiate (ACR) and right superior corona radiate (SCR). Then, we defined the CC genu and body, bilateral ACR, and right SCR as ROIs. We also extracted FA values from the ROIs and compared them between the MDD and HC groups using MANCOVA with age, sex, and education as covariates. Compared to those of the HC group, the MDD patients had significantly lower FA values in the CC genu (gCC, $p = 0.012$), the right ACR ($p = 0.001$) and the left ACR ($p = 0.002$) and showed a significantly decreased trend in FA values in the CC body ($p = 0.063$) (see Table S1 in Supplementary Material and Fig. 1).

3.3. Correlations between the FA values in the anatomical regions and clinical variables in the MDD patients

For FA values in the anatomical regions that significantly differed between the MDD and HC groups, we performed Pearson's partial correlation analysis to investigate their associations with clinical variables, such as the HDRS score and illness duration in the MDD group, after adjusting for age, gender, and education level. However, we did not find any significant correlations in the correlation analysis between the HDRS scores and FA values of the ROIs (CC genu and body, bilateral ACR) in the MDD patient group (all $p > 0.1$). Additionally, no significant correlations between the illness duration and FA values of the ROIs were found in the MDD patients (all $p > 0.1$) (See Table S2 in Supplementary Material).

3.4. Effect of the TPH2 genotype on the FA values in the MDD and HC groups

Within the MDD patients, at the uncorrected level, we found that the GG homozygote subgroup exhibited lower FA values than the T carriers (GT/TT) in many regions, including the CC genu ($x = 7$, $y = 24$, $z = 15$, voxels = 660), CC body ($x = 7$, $y = -1$, $z = 27$, voxels = 1622), right ACR ($x = 18$, $y = 38$, $z = -5$, voxels = 930), left

Table 1
Demographic and Clinical Characteristics of MDD and HC.

	MDD ($n = 118$)	HC ($n = 118$)	t/χ^2	p value
Gender (n, male/female)	37/81	39/79	0.078	0.781
Age (year)	33.37 ± 9.178	31.64 ± 9.970	1.438	0.167
Education level (year)	12.33 ± 4.231	15.29 ± 4.488	−5.029	<0.0001
Duration (months)	12.158 ± 15.759	–		
HDRS-17 score	23.73 ± 4.805	0.50 ± 0.650	52.039	<0.0001
HAMA score	22.69 ± 5.625	0.78 ± 0.775	41.92	<0.0001
TPH2 gene rs4570625 (n)				
GG	23	26	2.308	0.315
GT	50	58		
TT	45	34		
HWE	0.185	0.893		
GG	23	26	0.232	0.630
GT + TT	95	92		
G (allele frequency)	96	110	1.456	0.228
T (allele frequency)	140	126		

	MDD GG ($n = 23$)	MDD GT + TT ($n = 95$)	P value	HC GG ($n = 26$)	HC GT + TT ($n = 92$)	p value
Gender (male/female)	12/11	25/70	0.016	9/17	30/62	0.848
Age (year)	35.91 ± 10.042	32.76 ± 8.790	0.140	30.62 ± 9.745	31.93 ± 10.067	0.554
Education level (year)	10.78 ± 3.837	12.71 ± 4.255	0.050	15.31 ± 3.438	15.32 ± 4.622	0.994
Duration (months)	10.783 ± 17.040	12.497 ± 15.510	0.642	–	–	–
HDRS-17 score	22.70 ± 4.856	23.98 ± 4.785	0.252	0.42 ± 0.703	0.55 ± 0.669	0.384
HAMA score	22.43 ± 4.561	22.76 ± 5.874	0.806	0.92 ± 0.796	0.71 ± 0.768	0.287

Data for clinical characters are expressed as means ± standard error.
The p-value for distributions of gender, TPH2 genotype and allele frequency were obtained by chi-square test.
The p-values for the continuous variables were obtained by independent t-tests.
MDD = major depressive disorder; HC = healthy control; HDRS = Hamilton Rating Scale for Depression; HAMA = Hamilton Anxiety Scale; GG/GT/TT: genotype of TPH2 gene rs4570625 polymorphism; HWE = Hardy-Weinberg equilibrium.

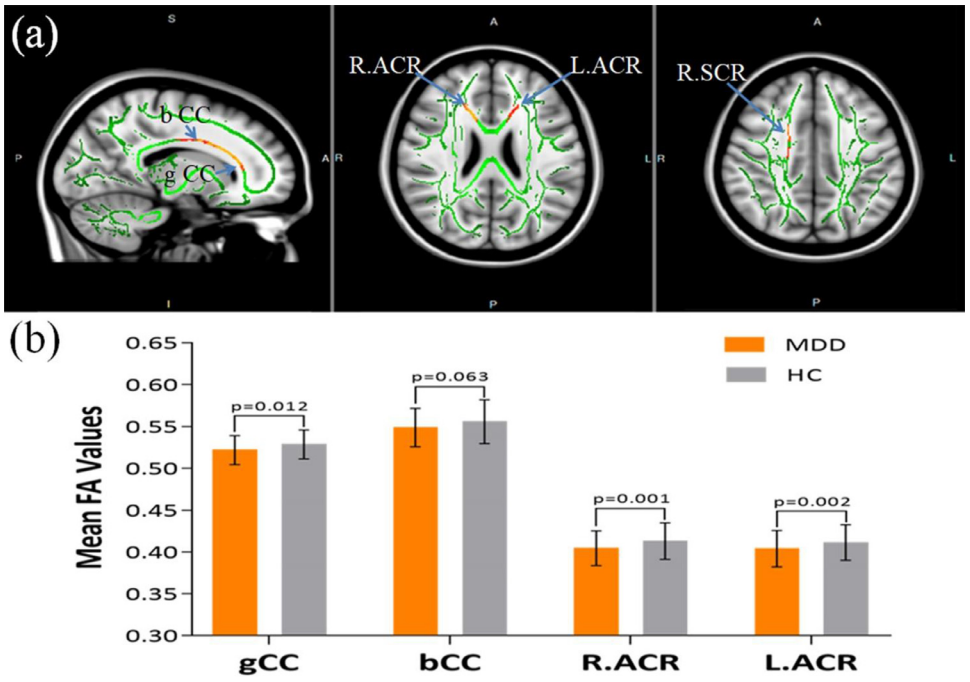

Fig. 1. Alterations in white matter FA between HC and first-episode, medication-naive patients with MDD. (a) Results of TBSS analysis showing significantly decreased FA values in MDD in bCC and gCC, bilateral ACR and right SCR (Family-wise error corrected, $p < 0.05$, voxel > 50). The background images are the mean FA map across all participants and the green voxels represent the mean FA skeleton image. The red-yellow voxels represent the white matter regions in which FA values were significantly decreased in MDD compared with the healthy controls. (b) ROIs analysis for the mean FA values in gCC, bCC and bilateral ACR.

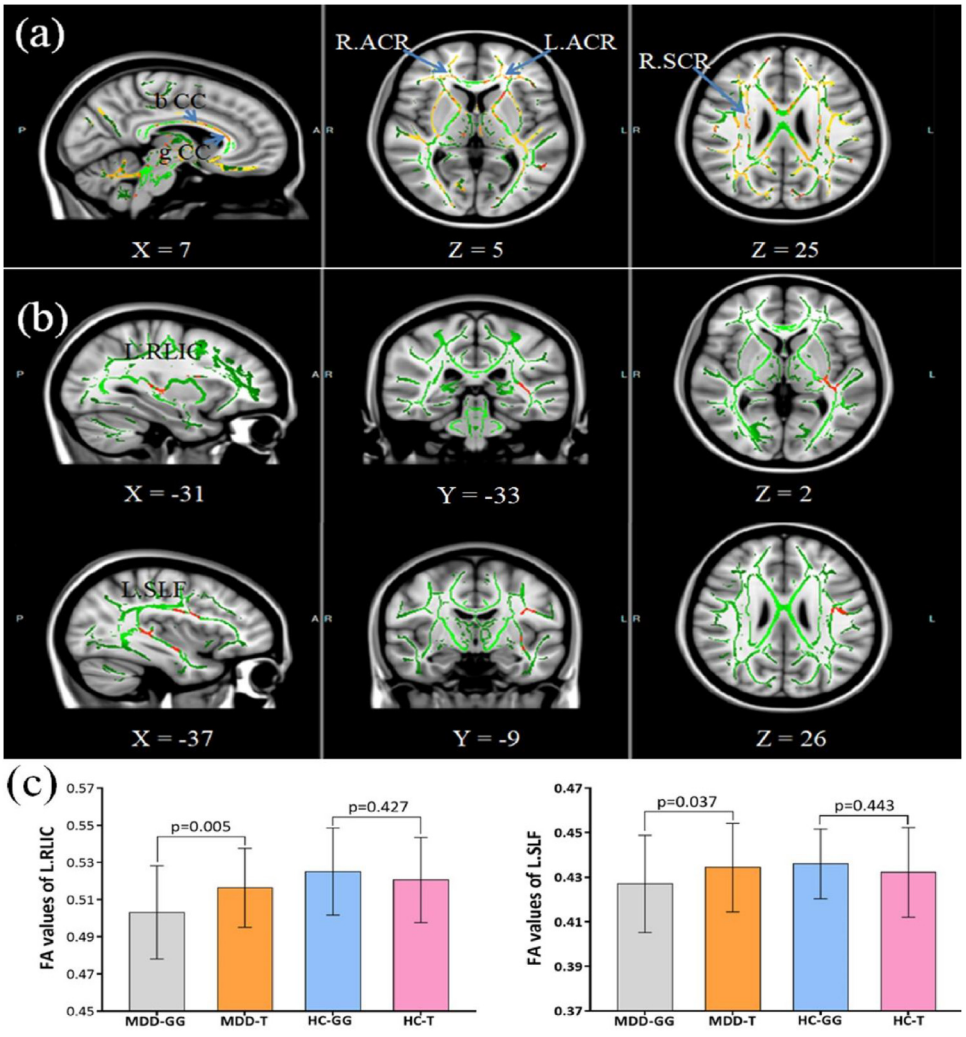

Fig. 2. Alterations in white matter FA between different genotype subgroup within MDD at different corrected level. (a) Results of TBSS analysis showing widespread reduction of FA in many white matter regions (uncorrected $p < 0.05$). Some regions were overlapped with the anatomical regions found in comparison between MDD group and HC group. (b) Results of TBSS analysis showing significantly decreased FA values in left RLIC and left SLF in GG homozygote subgroup compared to T carrier (GT/TT genotype) subgroup in patients with MDD (FWE corrected $p < 0.05$, voxel > 50). (c) Comparison of FA values of the left RLIC and left SLF among groups determined by diagnosis and the genotype. Error bars represent standard error of FA value. (MDD-GG, patients with GG genotype of rs4570625; MDD-T, patients T carrier genotype of rs4570625; HC-GG, healthy controls with GG genotype of rs4570625; HC-T, healthy controls with GT or TT genotype of rs4570625).

Table 2
Brain regions showing significant decrease of FA value in GG homozygote group compared to T carrier (GT/TT genotype) group in patients with MDD.

Anatomical region (voxels > 100)	voxels	MNI peak coordinates (mm)			*F*	*p*-value
		X	*Y*	*Z*		
L. retrolenticular portion of the internal capsule	399	−31	−33	2	8.199	0.005
L. superior longitudinal fasciculus	247	−37	−9	26	4.450	0.037

R: right hemisphere; L: left hemisphere.
The *F* and *p* values were obtained using multivariate analysis of covariance adjusted for age, gender, education level as covariates.

ACR ($x = -16$, $y = 36$, $z = -5$, voxels = 1083) and right SCR ($x = 28$, $y = -11$, $z = 25$, voxels = 965) (see Fig. 2a). These regions overlapped with the anatomical regions found in the comparison between the MDD and HC groups. At a corrected level, only the FA values in left retrolenticular portion of the internal capsule (RLIC) ($x = -31$, $y = -33$, $z = 2$, voxels = 399) and the left superior longitudinal fasciculus (SLF) ($x = -37$, $y = -9$, $z = 26$, voxels = 247) remained significantly lower after correcting for multiple comparisons at the threshold of an FWE-corrected $p < 0.05$ and voxel > 100 in the GG homozygote subgroup than in the T-carriers (see Fig. 2b). Then, we extracted individual FA values in the left RLIC and left SLF regions and performed MANCOVA with age, sex, and education as covariates across subgroups. The GG homozygote subgroup showed a significant reduction in FA in the left RLIC ($p = 0.005$) and left SLF ($p = 0.037$) compared with those of the T carrier subgroup (See Fig. 2c and Table 2)

No significant difference was observed when the FA values were compared between different genotype subgroups within the healthy control group.

4. Discussion

To the best of our knowledge, the present report demonstrated an association between the TPH2 gene rs4570625 polymorphism and the white matter microstructure of patients with first-onset untreated MDD for the first time. Similar to previous reports, we showed a significant reduction in FA in WM regions, including CC genu and body and the bilateral ACR, in the MDD patient group compared to those of the controls. The CC is the largest fiber bundle connected with the bilateral cerebral hemispheres and plays an important role in integrating the motor, sensory, and cognitive functions of the brain (Lacerda et al., 2005; Xu et al., 2013). Specifically, the prefrontal and orbitofrontal regions are connected by the CC genu, and the precentral frontal regions and parietal lobes are connected by the CC body (Liao et al., 2013; Xu et al., 2013). Demyelination of the CC genu and body may result in functional impairment of frontal lobe information transfer between hemispheres (Brambilla et al., 2004), leading to emotional regulation, memory and cognitive function defects (Han et al., 2014; Tham et al., 2011; Yamada et al., 2015). A number of recent meta-analyses of depression and DTI studies have found reductions in the FA values of the CC in patients with MDD (Chen et al., 2017, 2016; Jiang et al., 2017); one of these studies reported a significant FA reduction in the CC body in first-onset, drug-free patients with MDD (Chen et al., 2017). In addition, several other studies also revealed significantly decreased FA values in the CC body in first-episode, medication-naïve MDD patients (Han et al., 2014; Won et al., 2016; Xiao et al., 2015). These consistent results suggest that the corpus callosum may play an important role in the pathophysiology of depression. The decreased FA in the CC may be associated with deficits of working memory and attention in patients with depression (Yamada et al., 2015) and may underlie the impairment in emotional regulation and cognitive processing in MDD (Jiang et al., 2017). In summary, the reductions in FA in the CC genu and body found in our present study were consistent with previous reports on structural abnormalities of the CC suggested by neurological imaging studies in depression (Jiang et al., 2017; Won et al., 2016). This evidence further supports the hypothesis that abnormal structural integrity in the CC may be a promising neurophysiological marker associated with the pathogenesis of depression. Meanwhile, the ACR is a key structural component of the limbic-thalamo-cortical circuitry that plays a major role in emotional regulation involved in the pathophysiology of MDD (Drevets et al., 2008). Several studies have shown that the functions of the executive attention network may be related to the WM integrity in the ACR (Niogi et al., 2010; Yin et al., 2013). These findings indicate that abnormal white matter integrity in the ACR can lead to cognitive and emotional management disorders that affect MDD progression through brain circuitry associated with cognitive control. Additionally, decreased FA values in the ACR have been suggested by previous DTI studies in adult and adolescent MDD patients (Henderson et al., 2013; Lewinn et al., 2014). The above evidence and our findings of lower fractional anisotropy in the ACR support the hypothesis that impaired integrity in the ACR may be associated with MDD.

Specifically, in the comparison of the different MDD genotype subgroups, we observed that G homozygous subjects exhibited a widespread reduction of FA in brain regions compared to that of the T allele carriers at the uncorrected level, which was in line with the results found in the comparison between the MDD patients and controls. The FA values remained particularly significantly lower in the left RLIC, which carries optic tracts, including the geniculocalcarine radiations and left SLF, after correcting for FWE multiple comparisons. Although the findings were inconsistent at the different corrected levels, the results at the uncorrected level demonstrated evidence indicating an association between genetics and structural alterations in the brain of depressed patients to some extent. Further studies are needed to confirm these findings in the future. As for results at the corrected level, previous reports have also shown reductions in FA in the left RLIC (Guo et al., 2012; Xiao et al., 2015) and left SLF (Jiang et al., 2017; Lai and Wu, 2014; Shen et al., 2017) of patients with depression. Abnormalities of the WM tracts in the internal capsule may reflect dysfunction of the cortical-subcortical neural circuits that underlie the pathophysiology of MDD (Zhu et al., 2011). The SLF, which is a part of the association fibers, is a vital mediator within neural circuits of the prefrontal cortex and other lobes and the limbic system. Moreover, reduced integrity in the SLF may be a significant feature of the neuropathology of MDD and may underlie deficits of the emotional process and cognitive function in MDD (Murphy and Frodl, 2011). A meta-analysis study also ascertained that impairments in the WM microstructure of the SLF might be another important biomarker for the pathogenesis of depression (Jiang et al., 2017). To date, whether the TPH2 rs4570625 polymorphism has a direct effect on the TPH2 expression rate and activity has not been clearly defined. Although Chen et al. (2008) and Lin et al. (2007) showed that SNPs had a significant effect on TPH2 expression in vitro, Scheuch et al. (2007) did not confirm this finding. However, some studies have assumed that the TPH2 GG and T variants have different promoter activity and may be associated with TPH2 mRNA expression levels (Lim et al., 2007), with T-carriers exhibiting decreased TPH2 gene transcription and expression in the raphe nuclei, leading to a lower serotonin level (Markett et al., 2017). Additionally, serotonin (5-hydroxytryptamine, 5-HT) plays a vital role during mammalian brain development (Janusonis et al., 2004; Whitaker-Azmitia, 2001), provides negative feedback to its own neurons and sets its own terminal density. Previously, 5-HT depletion has been shown to be related to alterations in brain morphology (Vitalis et al., 2007), including both grey and white matter structures (Howell et al., 2014). Hence, based on the above evidence, one possible explanation for our findings may be that GG homozygotes are likely to have higher TPH2 gene transcription and expression levels and consequently increased central serotonin levels during brain development. Due to the effect of negative feedback,

these phenomena may ultimately result in lower 5-HT terminal levels and further interact with proinflammatory cytokines or other factors, promote myelin damage and eventually lead to white matter microstructural abnormalities.

Consistent with previous research (Guo et al., 2012), we also did not find any significant correlations between the FA values of the ROIs and clinical characteristics, including symptom severity and illness duration, in the MDD group. However, some of the literature reported that clinical variables, such as the illness duration and/or symptom severity, were related to abnormal FA values in MDD patients (Han et al., 2014; Tha et al., 2013; Yang et al., 2017). The finding of a lack of correlation may be confounded by heterogeneity of the sample size, age of the patients, MDD symptom dimensions, and disease stages. Image acquisition and data analysis were partly responsible for the heterogeneity of the results. The inconsistent results indicated that the correlation between WM alternations and clinical characteristics might need to be clarified in the future.

Although the possible effects of psychotropic medication on brain microstructure were excluded by recruiting first-episode, medication-naïve without other mental illnesses, some limitations in this study should still be addressed. First, we only explored one SNP, but multiple genetic polymorphisms might be associated with WM abnormalities in MDD. Second, we did not assess the effects of environmental factors (e.g. childhood adversity or maltreatment), which were found to influence white matter integrity (Lewinn et al., 2014; Ugwu et al., 2015). Therefore, the influence of these environmental factors on our results is uncertain and should be examined in further studies. Third, the current study is a cross-sectional observational study. Further longitudinal follow-up studies may be necessary to show how the abnormal brain area changes with disease development.

In conclusion, our study revealed that first-onset, untreated MDD patients had significant and robust decreases in the integrity in the CC genu and body and the bilateral ACR. Furthermore, our study provides evidence for the influence of the TPH2 gene on alterations in WM integrity in depression. These results demonstrate that the TPH2 rs4570625 gene may play an important role in white matter structural changes and may help illuminate the neurophysiological mechanisms of MDD.

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Conflict of interest

There is no conflict of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.02.002.

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