

White Matter Alterations Associated with Pro-inflammatory Cytokines in Patients with Major Depressive Disorder

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Objective: Regarding the neuroinflammatory theory of major depressive disorder (MDD), little is known about the effect of pro-inflammatory cytokines on white matter (WM) changes in MDD. We aimed to investigate the relationship between pro-inflammatory cytokines and WM alterations in patients with MDD.

Methods: Twenty-two patients with MDD and 22 healthy controls (HC) were evaluated for brain imaging and pro-inflammatory cytokines including interleukin (IL)-1 β , IL-6, IL-8, interferon- γ and tumor necrosis factor (TNF)- α . Tract-based spatial statistics and FreeSurfer were used for brain image analysis.

Results: The levels of TNF- α and IL-8 were significantly higher in the MDD group than in HC. Compared to HC, lower fractional anisotropy (FA), and higher median diffusivity (MD) and radial diffusivity (RD) values were found in the MDD group for several WM regions. Voxel-wise correlation analysis showed that the level of TNF- α was negatively correlated with FA, and positively correlated with MD and RD in the left body and genu of the corpus callosum, left anterior corona radiata, and left superior corona radiata.

Conclusion: Our findings suggest that TNF- α may play an important role in the WM alterations in depression, possibly through demyelination.

KEY WORDS: Depressive disorder, major; Cytokines; Tumor necrosis factor-alpha; White matter; Neuroimaging; Corpus callosum.

INTRODUCTION

Major depressive disorder (MDD) is a heterogeneous disease involving widespread disruptions in functional brain networks. While the most widely accepted hypothesis for the pathogenesis of MDD is the monoamine theory [1], the neurobiological mechanisms of MDD are still poorly understood. Even though various antidepressants such as selective serotonin receptor inhibitors, serotonin-norepinephrine receptor inhibitors, and norepinephrine dopamine receptor inhibitors were developed based on the monoamine theory and widely used for patients with MDD, still one-third of the patients fail to respond to

antidepressant treatment [2].

Neuroinflammation has been proposed as a pathogenesis theory to explain the heterogeneity and complex feature of depression [3]. Persons who are infected by virus or bacteria experience 'sickness behavior' such as anhedonia, fatigue, anorexia, and impaired sleep similar with symptoms of depression, which are induced by pro-inflammatory cytokines – interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)- α [4]. Peripheral cytokines are transmitted to the brain by humoral, neural, and cellular routes [3,5], which could affect neurotransmitter signaling resulting in behavioral changes. A higher prevalence of depression in patients with chronic inflammatory diseases also supports the relationship between depression and inflammation [6]. In a similar vein, several studies have reported the relationship between MDD and inflammatory cytokines [7-9], including meta-analysis studies showing that inflammatory cytokines in patients with MDD are significantly higher than healthy controls (HC) [10,11]. Various

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cytokines are listed, but increased levels of TNF- α or IL-6 in patients with MDD are the most common results [10,11]. Miller *et al.* [12] exhibited pro-inflammatory cytokines to act a crucial role in the pathogenesis of MDD, even suggesting peripheral blood levels of IL-1 β , IL-6, and TNF- α as biomarkers of inflammation in MDD patients.

Cytokines can disrupt the maturation of oligodendrocytes, resulting in an alteration of white matter (WM) development [13]. Oligodendrocytes, responsible for myelin-producing in the brain, are particularly vulnerable to inflammation compared to other cell types in the brain [14]. For instance, TNF- α can induce the death of oligodendrocytes directly by binding to TNF receptor p55 [15]. Interferon (IFN)- γ is also known to be highly toxic to oligodendrocytes [16]. This highly susceptible nature of oligodendrocytes could explain primary demyelination due to nonspecific immune reactions, observed in many inflammatory diseases [17,18].

With the development of brain imaging technology, WM microstructural changes can be detected by researching connectivity indexes such as fractional anisotropy (FA), radial diffusivity (RD), and mean diffusivity (MD), through diffusion tensor imaging (DTI) [19]. Previous DTI studies have shown that WM alterations are observed in various regions among patients with MDD [20-22]. Recently, Enhancing Neuro Imaging Genetics through Meta-Analysis consortium, a worldwide group for analyzing brain imaging, reported robust results indicating the corpus callosum (CC) and corona radiata (CR) to be the most prominent regions showing WM microstructural changes in MDD [23].

However, there is a scarce amount of research on the relationship between cytokines and WM alterations in major depression. Only one previous study showed that IL-1 β was associated with reduced FA [24], but there was no difference in cytokine levels between patients with depression and normal controls. Therefore, this study aimed to investigate the difference in pro-inflammatory cytokine levels between patients with MDD and HC, and whether increased levels of pro-inflammatory cytokines influenced brain WM microstructure in MDD patients.

METHODS

Participants

All patients with MDD were recruited at the CHA

Bundang Medical Center between October 2015 and April 2017. HC subjects were also recruited for the same period by a public advertisement. Experienced psychiatrists (B.K., H.S.) performed a diagnosis of MDD based on the Mini International Neuropsychiatric Interview [25,26]. Patients who met the criteria of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision were enrolled. The exclusion criteria included the diagnosis of other major psychiatric disorders (e.g., schizophrenia, bipolar affective disorder, schizoaffective disorder or intellectual disability), any history of neurological disease or serious physical disease (e.g., organic mental disorder, cancer, etc.), alcohol or drug dependence, and the presence of contraindications to brain magnetic resonance imaging (MRI).

Twenty-two patients with MDD and 22 HC participants were enrolled for this study from the participant pool of previous study [27]. All participants were 17–70 years old, of Korean descent, and right-handed. All patients were assessed by the Hamilton Depression Rating Scale [28,29] at baseline. Furthermore, all participants were scored based on the Beck Depression Inventory [30,31] and Beck Anxiety Inventory [32,33] at the time of enrollment. All subjects in this study were either medication-naïve (HC $n = 22$; MDD $n = 14$) or -free (MDD $n = 8$) for at least 9 weeks at the time of enrollment (Supplementary Tables 1, 2; available online).

All research procedures were performed under the review of the Institutional Review Board of CHA Bundang Medical Center, CHA University (no. BD 2015-088), and all participants were provided written consent after receiving a full description of the study.

Biochemical Analyses

We collected blood samples from all participants immediately after enrollment and before the initiation of antidepressant administration in the case of patients. Venous blood samples (6 ml) were drawn from each participant in gel tubes and processed in the laboratory immediately after collection. Serum cytokine (IL-1 β , IL-6, IL-8, IFN- γ , TNF- α) levels were measured using Bio-Rad Bio-Plex[®] assay (Bio-Rad, Hercules, CA, USA). The cytokine levels were measured and analyzed according to the manufacturer's instruction. Any value that was below the limit of detection (LOD) for the cytokine assay was replaced with half of the LOD of the assay, which is following a ro-

bust and well-established method [24,34].

Magnetic Resonance Imaging Acquisition

All MRI scans were acquired on a 3T GE Signa HDxt scanner (GE Healthcare, Milwaukee, WI, USA). Parameters for three-dimensional T1-weighted fast spoiled gradient recalled echo (3D T1-FSPGR) imaging were as follows: repetition time (TR) = 16 ms, echo time (TE) = 4.3 ms, flip angle = 10°, field of view (FOV) = 25.6 cm, matrix = 256 × 256, slice thickness = 1.7 mm, and isotropic voxel size = 1 × 1 × 1 mm³. Diffusion-weighted images were acquired using an echo-planar imaging sequence with the following parameters: TR = 17,000 ms, TE = 108 ms, FOV = 24 cm, matrix = 144 × 144, slice thickness = 1.7 mm, and voxel size = 1.67 × 1.67 × 1.7 mm³. We used the double-echo option to reduce the eddy-current-related distortions. To reduce the impact of spatial distortions, an 8-channel coil and an array of spatial sensitivity encoding technique (ASSET; GE Healthcare) with a sensitivity encoding speed-up factor of 2 was used. Seventy axial slices were acquired parallel to the anterior commissure-posterior commissure line covering the whole brain in 51 directions with $b = 900$ s/mm². We also acquired eight baseline scans with $b = 0$ s/mm². The least-squares method is used to estimate the DTIs from diffusion-weighted images.

Image Processing

For voxel-wise analysis of FA data, we used Tract-Based Spatial Statistics (TBSS), version 1.2, implemented in the FMRIB Software Library (FSL), version 5.0 according to standard procedures described below [35]. First, we used the FSL to perform DTI preprocessing, including skull stripping using the Brain Extraction Tool and Eddy current correction. Second, diffusion tensor values were calculated for each voxel using a least-square fit to the diffusion signal. Last, individual FA, MD, and RD metrics were derived from the three-dimensional maps using FMRIB's Diffusion Toolbox.

The FA data of all participants were aligned into the standard space (Montreal Neurologic Institute 152 standard) using the FMRIB Nonlinear Image Registration Tool. All transformed FA images were combined and applied to the original FA map, and this resulted in a standard-space version FA map. Then these FA images were averaged to create a mean FA image, which was subsequently thinned (skeletonized) to create a mean FA skeleton, taking only

the centers of the WM tracts. The threshold of the skeleton was $FA > 0.2$ (TBSS default) to include only major fiber bundles. FA images were used to achieve non-linear registration/skeletonization stages, to estimate the projection vectors from each participant onto the mean FA skeleton, and to compare the MD and RD.

FreeSurfer software, version 6.0.0 (Massachusetts General Hospital, Boston, MA, USA, <http://surfer.nmr.mgh.harvard.edu>) was used to obtain the estimated total intracranial volume (eTIV) with the 3D T1-FSPGR images. The eTIV was calculated using the automated tool for measuring the volume of brain structures, which is implemented in FreeSurfer and has been validated in several studies [36,37].

Statistical Analysis

Voxel by voxel statistical analysis was performed to detect regions with significant differences in FA, MD, and RD between the MDD and HC groups using nonparametric permutation tests with a correction for multiple comparisons with the FSL Randomise tool [38]. To achieve accurate inference, we used a permutation-based nonparametric inference within the framework of the general linear model tested with 10,000 permutations, including a full correction for multiple comparisons over space; $p < 0.05$ was considered statistically significant. Multiple comparisons were corrected with threshold-free cluster enhancement [39] to avoid making an arbitrary choice of the cluster-forming threshold while preserving the sensitivity benefits of the cluster-wise correction. Furthermore, analysis of covariance was conducted to adjust the effect of other variables, including age, sex, and eTIV on the results.

Correlation analyses were conducted to investigate whether the regional differences in FA and MD, RD could be potentially associated with the cytokine levels in each diagnostic group. For this purpose, the DTI data were analyzed using the TBSS General Linear Model regression analysis, with the cytokine levels as the variable. Clusters with 100 or more contiguous voxels were only considered in the analysis to reduce the possibility of false-positive results. We used the International Consortium for Brain Mapping-DTI-81 white-matter labels atlas of Johns Hopkins University DTI-based white-matter atlases [40,41] and the Talairach atlas [42,43] to identify altered regions.

An independent *t* test was used to compare continuous

Table 1. Characteristics of patients with MDD and HC

Variable	MDD (n = 22)	HC (n = 22)	<i>t</i>	<i>p</i> value
Sex, male/female	7/15	10/12		0.353 ^a
Age (yr)	39.32 ± 14.48	39.23 ± 11.82	0.023	0.982
eTIV (mm ³)	1,455,779.23 ± 126,962.78	1,507,458.37 ± 131,894.39	-1.324	0.193
IL-1β levels (pg/ml)	0.48 ± 0.06	0.02 ± 0.00	2.126	0.046 ^b
IL-6 levels (pg/ml)	0.97 ± 3.64	0.18 ± 0.28	1.012	0.323
IL-8 levels (pg/ml)	3.27 ± 2.01	1.31 ± 1.70	3.501	0.001 ^c
IFN-γ levels (pg/ml)	0.27 ± 0.47	0.11 ± 0.26	1.393	0.173
TNF-α levels (pg/ml)	6.83 ± 3.12	3.07 ± 3.23	3.922	< 0.001 ^c
HAMD total score	18.23 ± 5.36	-		
BDI total score	20.89 ± 7.68	4.81 ± 5.04	7.114	< 0.001 ^c
BAI total score	18.31 ± 10.98	2.44 ± 3.22	5.55	< 0.001 ^c

Values are presented as number only or mean ± standard deviation.

MDD, major depressive disorder; HC, healthy controls; eTIV, estimated total intracranial volume; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

^aChi-square test. ^b*p* < 0.05 without multiple comparison correction. ^cBonferroni correction *p* < 0.01.

variables, and the Pearson chi-squared test was used to analyze categorical variables. Multiple comparisons were performed using Bonferroni correction in the analysis of comparing cytokine levels between two groups. Statistical analysis was performed using SPSS 26.0 (IBM Co., Armonk, NY, USA), and *p* < 0.05 was considered statistically significant.

RESULTS

Characteristics of Study Participants

Table 1 presents the characteristics of the study participants. There were no significant differences between patients with MDD and HC for age, sex, and eTIVs. After multiple comparison correction, TNF-α and IL-8 showed significant differences between the two groups. In contrast, there were no statistically significant differences for the other cytokines such as IFN-γ and IL-6 between the two groups.

Comparison of White Matter Connectivity between Major Depressive Disorder Patients and Healthy Controls

The FA values obtained by TBSS analysis showed that patients with MDD have significantly lower FA than HC in various regions. The following regions are depicted in Figure 1: the body and genu of the CC, bilateral superior corona radiata (SCR), bilateral anterior corona radiata (ACR), and bilateral superior longitudinal fasciculus (SLF) (Fig. 1A). Age, sex, and eTIV were included as covariates

in the analysis. Significant differences between the two groups were also found for MD (Fig. 1B) and RD values (Fig. 1C).

Correlation Analyses between White Matter Connectivity and Cytokine Levels

We conducted voxel-wise correlation analyses between cytokine levels and FA, MD, and RD values of the WM clusters that showed significant group differences in each diagnostic group. Only TNF-α showed correlations with WM integrity but the other cytokines showed no correlation. In patients with MDD, the TNF-α level showed negative correlations with FA values of the following WM regions (Fig. 2A): left ACR, left SCR, body, and genu of CC. The TNF-α levels showed positive correlations with MD (Fig. 2B) and RD values (Fig. 2C) in WM regions showing negative correlations with FA values. In the HC, there was no significant correlation between the level of TNF-α and FA, MD, or RD values.

DISCUSSION

Antidepressant treatment based on the monoamine theory, although being the current mainstream treatment of MDD, has shown to result in more than 30% of patients failing to achieve remission despite multiple treatment trials [2]. Also, the monoamine theory alone cannot fully describe the complex characteristics of depression [3]. Therefore, the identification of alternative pathogenetic mechanisms of MDD, related potential biomarkers and

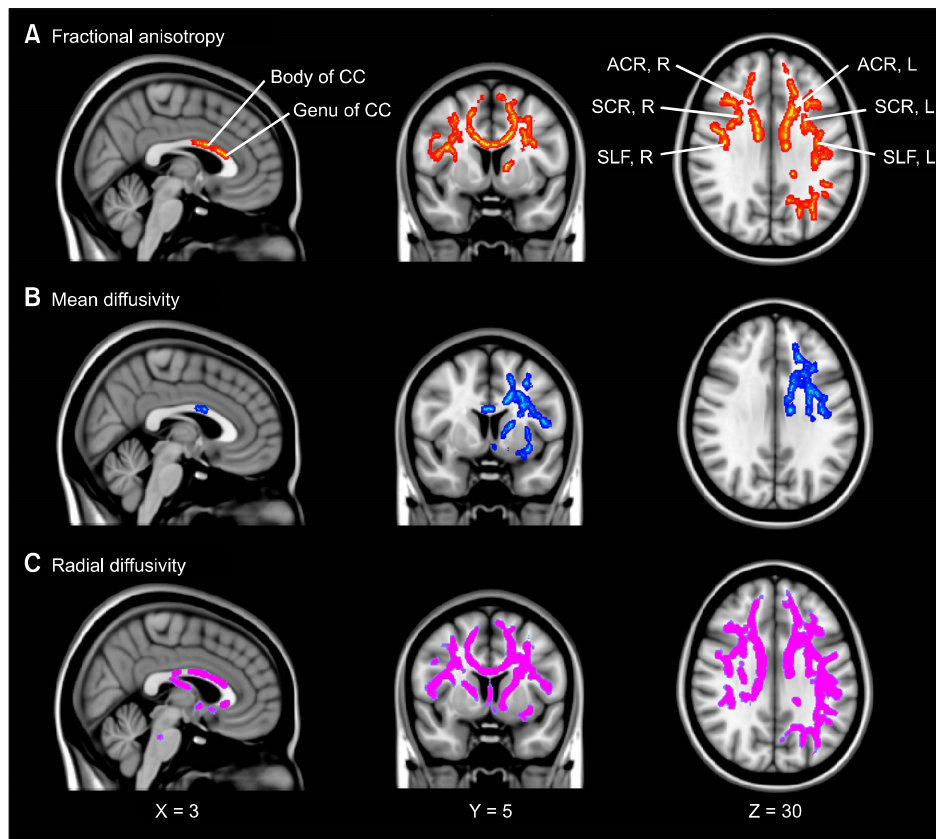


Fig. 1. Voxel-wise analysis showing significant differences (threshold-free cluster enhancement-corrected $p < 0.05$) between patients with major depressive disorder (MDD) and healthy controls (HC). (A) The regions showing significantly decreased fractional anisotropy in patients with MDD compared to HC are depicted in red-yellow. (B) The regions showing significantly increased mean diffusivity in patients with MDD compared to HC are depicted in blue-light blue. (C) The regions showing significantly increased radial diffusivity in patients with MDD compared to HC are depicted in light blue-purple. Results are shown overlaid on the Montreal Neurologic Institute 1-mm template. R, right; L, left; ACR, anterior corona radiata; CC, corpus callosum; SCR, superior corona radiata; SLF, superior longitudinal fasciculus.

neurobiological targets of novel therapeutic options, is needed. One of the candidate mechanisms in this regard is neuroinflammation and associated increases in cytokine levels. We hypothesized a significant difference in pro-inflammatory cytokine levels would exist between patients with MDD and HC, and this would in turn lead to alterations in WM connectivity. We observed decreased FA values of the CC, bilateral SCR, ACR, and SLF, in patients with depression patients compared to HC. Our results are in line with a previous study published from our lab [27] and other studies reporting WM alterations in patients with MDD [44,45]. Our results also showed TNF- α levels to be negatively correlated with FA values of the left SCR, left ACR, body, and genu of CC, in the MDD patient group. To our knowledge, this is the first study to report correlations between TNF- α levels and WM connectivity in patients with MDD.

According to the previous DTI studies, the reduced FA values reflect WM abnormalities [20]. Also, elevations in the RD values are known to be associated with demyelination or dysmyelination, and higher MD values can be related to the increased level of tissue water often due to inflammation [46]. Thus, it can be assumed that alterations in WM regions showing the decreased FA, and increased MD and RD values are associated with tissue water increase and myelination deficits, which have been observed in patients with MDD [20] and other demyelinating diseases, such as multiple sclerosis [47].

Our results showed an increased level of pro-inflammatory cytokines, such as TNF- α and IL-8 in patients with MDD than HC, which is in conjunction with other studies regarding neuroinflammation [10,48,49] including a meta-analysis showing higher TNF- α level in MDD [11]. According to Tarkowski *et al.* [50], TNF- α is one of

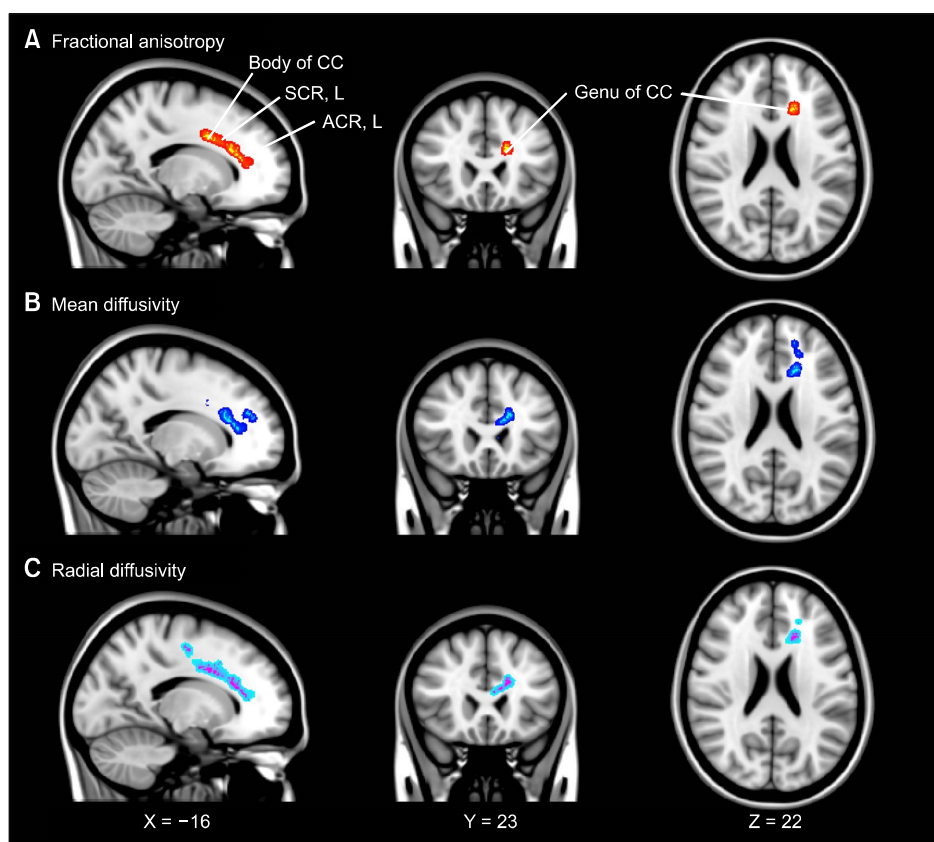


Fig. 2. Voxel-wise analysis showing significant correlations (threshold-free cluster enhancement-corrected $p < 0.05$) between tumor necrosis factor (TNF)- α levels and fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) in patients with major depressive disorder (MDD). (A) The regions showing significant negative correlations between TNF- α levels and FA values are depicted in red-yellow. (B) The regions showing significant positive correlations between TNF- α levels and MD values are depicted in blue-light blue. (C) The regions showing significant positive correlations between TNF- α levels and RD values are depicted in light blue-purple. The voxels showing significant differences between patients with MDD and healthy controls were used for correlation analyses. Images are shown overlaid on the Montreal Neurologic Institute 1-mm template.

L, left; ACR, anterior corona radiata; CC, corpus callosum; SCR, superior corona radiate.

the key cytokines in the immune system of central nervous system (CNS). The dynamic role of TNF- α in the brain has been studied in other psychiatric disturbances, such as Alzheimer's disease [50] and multiple sclerosis [51], which suggested TNF- α might affect brain structure to progress disease through demyelination and loss of oligodendrocytes [52]. Even though the mechanism of the loss of oligodendrocytes has not completely defined yet, it has been observed that TNF- α induces oligodendrocyte degeneration [15,53] through activation of microglia to produce Monocyte Chemoattractant Protein-1, attracting monocytes to the brain [54]. Considering the previous findings above, it can be assumed that TNF- α plays a crucial role in changes in oligodendrocytes, the myelinating cells of the CNS. Therefore, the current findings showing

decreased FA and increased MD and RD on several WM tracts and their significant correlations with TNF- α level can be related to inflammation-related alterations of WM myelination in patients with MDD.

In the present findings, higher TNF- α is correlated with lower FA of left ACR and SCR regions in patients with MDD. CR is the fan-shaped projection fibers linking the cerebral cortex to subcortical regions such as thalamus [55]. The ACR is a part of limbic-thalamo-cortical circuitry and is known to be associated with emotional regulation, one of the major affected functions in MDD [56,57]. Also, there are several pieces of research providing that microstructural change of ACR could be associated with many of core symptoms of depression by impairing communication between cortex and thalamus that is required

for emotional regulation and executive attention [58,59]. For example, Niogi *et al.* [60] reported that the FA of the ACR modulates executive attention, and is also correlated with attention network task. According to Choi *et al.* [45], MDD patients showed reduced FA in the ACR and PCR, which suggested the disruption of emotional and cognitive control networks as the pathophysiology of MDD. Similar to our findings, lower FA, and higher MD and RD of CR associated with inflammation-related cytokines have been observed in patients with bipolar depression [61].

We also have shown reduced FA of the body and genu of CC is correlated with higher TNF- α in patients with MDD. The CC is the largest commissural fibers connecting the left and right hemisphere, which develops mostly during childhood and adolescence, and keeps changing with aging [62]. The maturation of CC is mainly accomplished by axonal myelination related to the maturation of cognitive processes, and a disruption of this process may induce deficits in memory and executive functioning [63]. Especially the defect on genu of CC connecting to the prefrontal cortex was reported to contribute to the impaired inter-hemispheric connectivity, resulting in deficits in working memory and cognition [64]. Besides, the linkage among the genu of CC, anterior cingulate, and insula is a key component of the fronto-limbic connection whose dysfunction is associated with emotional and autonomic dysregulation in depression [57,65]. In line with our results for WM alterations of CC, lower FA of CC has been reported by other neuroimaging studies in various depression groups including late-onset depression [66], early-onset adolescent [64], and drug naïve patients [22]. Given that CC is known to be the most populated brain area by microglia [67] and oligodendrocytes, and the most vulnerable to damages [68], increased TNF- α could induce inflammatory changes, resulting in axonal damage by demyelination or oligodendrocyte apoptosis in the CC [69].

However, even though the IL-8 level was significantly higher in the MDD group, no significant results for the correlation analysis between IL-8 level and DTI metrics. There have been inconsistent results for the relationship between IL-8 and MDD. For example, Memon *et al.* [70] showed that the level of IL-8 was higher in the depression group, but it was negatively associated with the severity of depression. Also, a couple of recent meta-analyses showed

no difference in the level of IL-8 between patients with MDD and HCs [10,11]. IL-8 is known to have both pro- or anti-inflammatory functions depending on the concentration, which implies a higher and a lower level of IL-8 might work toward opposite directions [71]. Therefore, it would be possible that IL-8 might act as both the destructive and protective roles in the possible demyelination process, which may be associated with the positive results in group comparison and the negative results for correlation analysis in this study.

There are several limitations to the study. First, the sample size is relatively small. Although the sample size in this study was within a similar range with those of other DTI imaging studies [72,73], future studies with a larger sample size may be needed to confirm the findings. Second, all participants in the MDD group were medication-free, but not drug naïve. Since at the time of enrollment all participants are medication-free at least 9 weeks, we assumed that chance of medication effect to the level of cytokines or brain microstructures might be minimal. Third, this study was not designed to include other inflammatory indicators such as white blood cell counts, absolute neutrophil counts, and C-reactive protein. Even though we excluded any participants who have major physical diseases including infection or autoimmune diseases, it would be helpful to see those indicators in future studies. Lastly, our findings showed a significant correlation with cytokine levels and the WM integrity metrics, but it cannot be concluded as a causal relationship between them. We assumed pro-inflammatory cytokine levels might affect oligodendrocytes and demyelinating axons, but it may require further longitudinal studies to find out the causal relationship between pro-inflammatory cytokine and WM microstructural changes.

In conclusion, we report, for the first time, a significant association between TNF- α levels and WM alterations in patients with MDD. Our finding suggests that the increased level of TNF- α is associated with the WM integrity of CR and CC in patients with MDD. This study proposes that pro-inflammatory cytokine TNF- α might play an important role in the WM alterations of patients with depression. It would be needed for further studies to reveal the full function of TNF- α in neuroinflammation and TNF- α as a potential biomarker in MDD.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Jaehwa Lim, Hoyoung Sohn, Borah Kim. Data acquisition: Jaehwa Lim, Hoyoung Sohn, Borah Kim. Formal analysis: Jaehwa Lim, Hoyoung Sohn, Min-Soo Kwon. Funding: Borah Kim. Supervision: Borah Kim. Writing original draft: Jaehwa Lim. Writing review & editing: Jaehwa Lim, Borah Kim.

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