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Effects of Uric Acid on the Alterations of White Matter Connectivity in Patients with Major Depression

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Objective Uric acid is a non-enzymatic antioxidant associated with depression. Despite its known protective role in other brain disorders, little is known about its influence on the structural characteristics of brains of patients with major depressive disorder (MDD). This study explored the association between uric acid and characteristics of white matter (WM) in patients with MDD.

Methods A total of 32 patients with MDD and 23 healthy controls (HCs) were examined. All participants were scored based on the Beck Depression Inventory and Beck Anxiety Inventory at baseline. All patients were also rated with the Hamilton Depression Rating Scale. We collected blood samples from all participants immediately after their enrollment and before the initiation of antidepressants in case of patients. Tract-based spatial statistics were used for all imaging analyses.

Results Lower fractional anisotropy (FA) and higher radial diffusivity (RD) values were found in the MDD group than in the HC group. Voxelwise correlation analysis revealed that the serum uric acid levels positively correlated with the FA and negatively with the RD in WM regions that previously showed significant group differences in the MDD group. The correlated areas were located in the left anterior corona radiata, left frontal lobe WM, and left anterior cingulate cortex WM.

Conclusion The present study suggests a significant association between altered WM connectivity and serum uric acid levels in patients with MDD, possibly through demyelination.

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Key Words Depressive disorder, Uric acid, Oxidative stress, Antioxidants, White matter, Neuroimaging.

INTRODUCTION

Research on the pathogenesis of depression has long focused on monoamine hypothesis, according to which the imbalance of monoamines, such as dopamine, norepinephrine, and serotonin, plays a key role in the development of depression.[1-3] Considering that nearly one-third of patients with depression do not respond to conventional antidepressants,[4] other mechanisms underlying depression, such as endocrine disturbances[5-8] or immunological alterations,[9-11] have been studied to explain the various aspects of the disorder.[12] Oxidative stress has been associated with depression because of its regulation through the imbalance between antioxidant defense and free-radical production.[13,14] Moreover, various antioxidants, including uric acid, vitamin E, glutathione, and coenzyme Q10, have been associated with depression.[15-17] Among these, uric acid, which has been suggested as a natural antioxidant that can scavenge superoxides, can prevent the reaction of superoxide with nitric oxide, which leads to the formation of the strong oxidant peroxynitrite in humans for a prolonged period.[18] Thus, uric acid protects axons from damage, attenuates myelin vacuolization and demyelination, and inhibits nitrotyrosine formation.[19] Previous studies have demonstrated reduced uric acid levels in depression.[13,20-26] Thus, brain uric acid is suggested to protect against oxidative stress in depression, by suppressing inflammation, oxidative, and nitrosative stress (IO&NS) pathway.[27,28]

This action is possibly mediated via the white matter (WM),

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which is more vulnerable to oxidative stress than the gray matter (GM),[29] because its major components, oligodendrocytes, are highly sensitive to oxidative stress injury.[30] The association of uric acid with depression is further supported by the fact that antidepressant treatment restores the low uric acid levels.[20,22,24] The relatively elevated oxidative stress in patients with recurrent compared with those with first-onset depression[31] indicates the cumulative nature of stress.

In addition to biochemical and molecular biological advances associated with depression, brain imaging has revealed functional and anatomical alterations in individuals with depression. The prefrontal cortex, anterior cingulate cortex (ACC), and corpus callosum are among the regions associated with depression according to various functional and structural neuroimaging studies.[32-36]

However, little is known about the association of uric acid with the structural characteristics of the brain of patients with major depressive disorder (MDD). Therefore, we conducted the present study to investigate the association between uric acid and brain structure of patients with depression. We hypothesized that 1) the WM integrity of patients with MDD would differ from that of healthy controls (HCs), as previously reported; 2) the alterations in WM integrity would be associated with serum uric acid levels, in relation to the diagnosis of MDD; and 3) these alterations would be prominent in patients with recurrent depression.

METHODS

Participants

Patients with depression were recruited by advertising at the outpatient clinic of the Department of Psychiatry, CHA Bundang Medical Center, run by experienced psychiatrists. One patient was recruited via consultation at the same hospital. HC participants were recruited by a public advertisement from October 2015 to April 2017. Patients with depression who met the criteria of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[37] were enrolled after being diagnosed with MDD by an experienced psychiatrist on the basis of the Mini International Neuropsychiatric Interview (MINI).[38,39] The exclusion criteria for all participants were as follows: 1) history of schizophrenia, bipolar affective disorder, or schizoaffective disorder; 2) possibility of pregnancy or lactation; 3) organic mental disorder or intellectual disability; 4) alcohol or drug dependence, which requires hospitalization; 5) serious medical conditions (e.g., cancer, chemotherapy); and 6) contraindications to brain magnetic resonance imaging (MRI), such as metal implants.

Initially, 34 patients with MDD and 24 HC participants were recruited in this study. After excluding left-handed participants, 32 patients with MDD and 23 HCs were finally examined in this study. All participants were 17−70 years old, of Korean descent, and right-handed. All patients were assessed by the Hamilton Depression Rating Scale[40,41] at baseline. Furthermore, all participants were scored based on the Beck Depression Inventory[42,43] and Beck Anxiety Inventory[44,45] at the time of enrollment. In the case of patients, we recorded if the current depressive episode was first-onset (n=12) or recurrent (n=20). All analyzed patients were either medication-naive or -free for at least 9 weeks at the time of enrollment.

All research procedures were performed under the review of the Institutional Review Board (IRB) of CHA Bundang Medical Center, CHA University (IRB No. 2015-06-088) and all participants provided written consent after receiving a full description of the current study.

Biochemical analyses

We collected blood samples from all participants immediately after enrollment and before the initiation of antidepressants 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. The serum uric acid levels were measured with an enzymatic colorimetric assay and the Roche UA2 module of the Roche/Hitachi cobas 8000 c702 Chemistry Autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instruction.

MRI acquisition

All MRI scans were acquired using the same 3 T GE Signa HDxt scanner (GE Healthcare, Milwaukee, WI, USA), equipped with an 8-channel phase array head coil at CHA Bundang Medical Center, CHA University. The parameters for three-dimensional (3D) 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 mm^3. We acquired diffusion-weighted images 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 mm^3. We used the double-echo option to reduce the eddy-current-related distortions. An 8-channel coil and the array spatial sensitivity encoding technique (ASSET; GE Healthcare) with a sensitivity encoding (SENSE) speed-up factor of 2 was used to reduce the impact of spatial distortions. We acquired 70 axial slices parallel to the anterior commissure-posterior commissure line covering the whole brain in 51 directions with b=900 s/

mm^2. We also acquired eight baseline scans with b=0 s/mm^2. We used the least-squares method to estimate the diffusion tensor images (DTIs) from diffusion-weighted images.

Image processing

We used Tract-Based Spatial Statistics (TBSS), version 1.2 (the Analysis Group, FMRIB, Oxford, UK), implemented in the FMRIB Software Library (FSL),[46] version 5.0, to perform processing of the fractional anisotropy (FA) data according to standard procedures.[47] First, we used the FSL to perform DTI preprocessing, including skull stripping using the Brain Extraction Tool (BET) and Eddy current correction. By fitting a tensor model to the raw diffusion data, the FA images were created. The FA data of all participants were subsequently 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, resulting in a standard-space version FA map. Furthermore, all the transformed 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. To include only major fiber bundles, the skeleton was thresholded by FA >0.2 (TBSS default).

We used the FA images to achieve non-linear registration/skeletonization stages, to estimate the projection vectors from each individual participant onto the mean FA skeleton, and to compare the mean, axial, and radial diffusivity (MD, AD, and RD, respectively).

To obtain the estimated total intracranial volume (eTIV), we used the latest version (v6.0.0) of FreeSurfer software (Massachusetts General Hospital, Boston, MA, USA, http://surfer.nmr.mgh.harvard.edu) with the 3D T1-FSPGR images. The eTIV was calculated using the automated tool for measuring volume of brain structures, which is implemented in FreeSurfer and has been validated in several studies.[48,49]

Statistical analysis of the DTI data

To detect regions with significant differences in FA, MD, AD, and RD between the two diagnostic groups (MDD vs. HC), we performed a voxel-by-voxel statistical analysis, using nonparametric permutation tests with a correction for multiple comparisons with the FSL Randomise tool.[50] 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, to achieve accurate inference; $p<0.05$ was considered statistically significant. We corrected multiple comparisons with threshold-free cluster enhancement (TFCE),[51] which enabled us to avoid making a random choice of the cluster-forming threshold, while preserving the sensitivity benefits of the cluster-wise correction. Furthermore, analysis of covariance (ANCOVA), with age, sex, and eTIV as covariates, was conducted to adjust the effect of other variables on the results. The same methods were used to investigate the group differences between 1) the first-onset depression and HC groups, 2) the recurrent depression and HC groups, and 3) the first-onset depression and recurrent depression groups.

Correlation analyses were conducted to investigate whether the regional differences in FA and RD could be potentially associated with the serum uric acid levels in each diagnostic group. For this purpose, the DTI data were evaluated using the TBSS General Linear Model regression analysis, with the serum uric acid level as the variable. To further reduce the possibility of false-positive results, only clusters with more than 100 contiguous voxels were considered in the analysis. We used the International Consortium for Brain Mapping-DTI-81 white-matter labels atlas of Johns Hopkins University DTI-based white-matter atlases[52-54] and the Talairach atlas[55-57] to identify altered regions.

Statistical analysis of other variables

An independent t-test was used to compare continuous variables, and Pearson chi-squared test was used to analyze categorical variables. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 22.0 (IBM Corp., Armonk, NY, USA), and $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of study participants

Table 1 summarizes the characteristics of the study participants. No significant difference as observed in characteristics, including age and sex, between the MDD and HC groups. In contrast, the eTIVs were different between the two groups.

In addition, Supplementary Table 1 (in the online-only Data Supplement) summarizes the characteristics of the subgroups (i.e., the first-onset and recurrent depression groups). None of the characteristics, namely age, sex, and eTIVs, were significantly different.

TBSS results of WM

FA data

According to the TBSS analysis, the FA values were significantly lower in the depression than in the HC group. The analysis yielded one large cluster of significant (TFCE-corrected $p<0.05$) voxels on the WM skeleton (Supplementary Figure 1A in the online-only Data Supplement). The total

Table 1. Characteristics of the study participants

	Depression (N=32)	Healthy control (N=23)	t	p
Sex, male/female (N)	7/25	11/12		0.79*
Age (years)	41.06±13.76	38.91±11.65	0.608	0.546
eTIV (mm^3)	1431259.06±124009.99	1513135.98±131707.27	-2.354	0.022
Serum uric acid levels (mg/dL)	4.50±1.05	5.00±1.07	-1.712	0.093
HAMD total score	18.31±5.15	-		
BDI total score	21.18±7.48	4.81±5.04	7.78	<0.001
BAI total score	18.96±11.20	2.44±3.22	7.06	<0.001

Data are mean±standard deviation, except for the sex distribution. The p value for the sex distribution was obtained by chi-square test. The p values for age, eTIV, serum uric acid levels, HAMD, BDI, and BAI scores were obtained using the independent t test. *Fisher's exact test. BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, eTIV: estimated total intracranial volume, HAMD: Hamilton Depression Rating Scale

Table 2. Regions showing significant decreases in fractional anisotropy values in the depression group compared with the healthy control group by analysis of covariance, in which age, sex, and estimated total intracranial volume were included as covariates

Cluster size (voxels)	Peak coordinates (mm)*	Z	Anatomical locations	p†
19043	-8, -18, 26	5.22	Corpus callosum (body)	0.0353
	-9, -29, -20	5.22	Cerebral peduncle, left	0.0270
	44, -2, 32	5.1	Frontal lobe WM, right	0.0340
	-29, -5, 42	5.02	Frontal lobe WM, left	0.0157
	-22, 4, 26	4.68	Superior corona radiata, left	0.0283
	-17, 17, 30	4.34	Anterior corona radiata, left	0.0118
	17, 36, -6	4.24	WM in ACC, right, Anterior corona radiata, right	0.0244
	4, 20, 18	4.17	Corpus callosum (genu)	0.0158
	-22, -11, 6	3.85	Posterior limb of internal capsule, left	0.0222
	-28, -67, 1	3.83	Posterior thalamic radiation, left	0.0400
	-37, -9, 30	3.73	Superior longitudinal fasciculus, left	0.0163
	20, -11, 42	3.69	Superior corona radiata, right	0.0265
	-22, 9, 17	3.64	Anterior limb of internal capsule, left	0.0282
	-19, 39, 10	3.56	WM in ACC, left	0.0203
	-21, 8, 21	3.46	Superior fronto-occipital fasciculus, left	0.0279
	32, 6, 28	3.31	Superior longitudinal fasciculus, right	0.0361
	-31, -17, 13	3.23	External capsule, left	0.0294

*foci for significant differences are listed (corrected p<0.05), †threshold free cluster enhancement corrected p value. ACC: anterior cingulate cortex, WM: white matter

number of voxels, Z-values, peak coordinates, and anatomical locations are listed in Table 2. The cluster (19,043 voxels) was located in the body and genu of the corpus callosum, left cerebral peduncle, bilateral frontal lobe WM, bilateral superior corona radiata (SCR), bilateral anterior corona radiata (ACR), WM in the bilateral anterior cingulate cortex (ACC), anterior and posterior limbs of the left internal capsule, left posterior thalamic radiation (PTR), bilateral superior longitudinal fasciculus (SLF), left superior fronto-occipital fasciculus (SFO), and left external capsule. The age, sex, and eTIV were included as covariates in the analysis.

Non-FA (MD, AD, and RD) data

The RD values were significantly higher in the depression than in the HC group. From the TBSS analysis, we obtained one large cluster of significant (TFCE-corrected p<0.05) voxels on the WM (Supplementary Figure 1B in the online-only Data Supplement). The total number of voxels, Z-value, peak coordinates, and anatomical locations are listed in Supplementary Table 2 (in the online-only Data Supplement). The cluster (16,737 voxels) was located in almost identical regions as in the case of the FA data, namely the left external capsule, bilateral frontal lobe WM, bilateral SCR, bilateral ACC WM, bilateral ACR, genu and body of the corpus cal-

losum, anterior and posterior limbs of the left internal capsule, and bilateral SLF. Age, sex, and eTIV were included as covariates in the analysis. The MD and AD values were not significantly different between the MDD and HC groups. However, the MD values showed a trend for higher levels along the left frontal lobe WM, left SCR, left ACR, left external capsule, corpus callosum body, anterior and posterior limbs of the left internal capsule, left SLF, and left ACC WM (TFCE-corrected $p<0.1$, minimum TFCE-corrected $p=0.0728$) in the MDD than in the HC group (Supplementary Figure 2 in the online-only Data Supplement).

Correlation analyses

We performed voxelwise correlation analyses between the serum uric acid levels and the FA and RD values of the WM clusters that showed significant group differences. To investigate the relationship between the serum uric acid levels and the WM connectivity in each diagnostic group, correlation analyses were conducted in each group. In patients with MDD, the serum uric acid levels correlated positively with the FA (Figure 1A) and negatively with the RD values (Figure 1B). The FA data of the related brain regions are listed in Table 3 and the RD data, in Supplementary Table 3 (in the

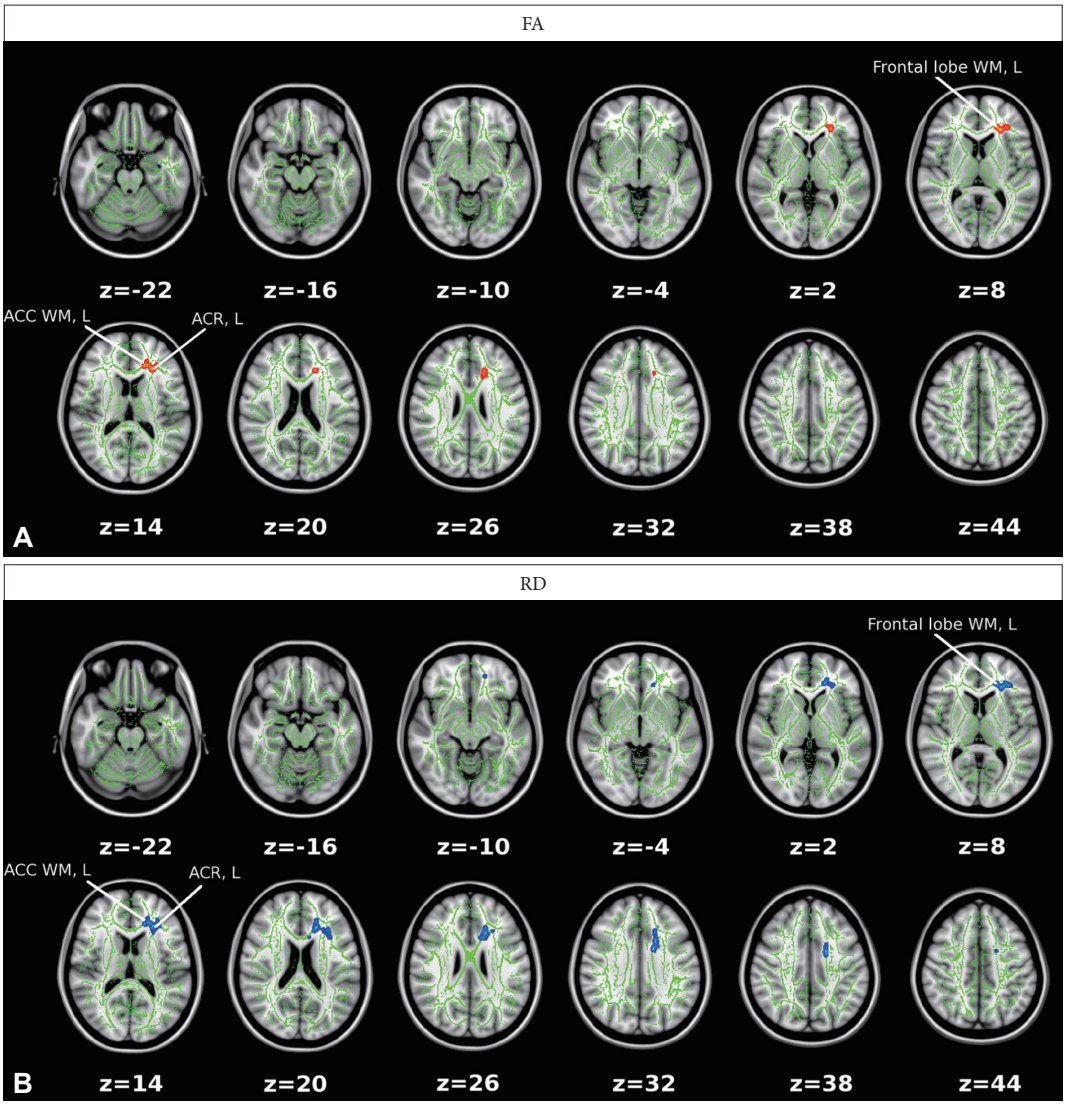

Figure 1. Tract-Based Spatial Statistics analysis showing significant correlations (corrected $p<0.05$) between the serum uric acid levels and FA or RD values in the depression group. A: Voxels demonstrating significant positive correlations between the serum uric acid levels and FA values in the depression group are shown in red-yellow. B: Voxels demonstrating significant negative correlations between the serum uric acid levels and RD values in the depression group are shown in blue-lightblue. Only voxels showing significant differences between patients with depression and healthy controls are included. Results are shown overlaid on the Montreal Neurologic Institute 1-mm template (Z=-22 to Z=44) and the mean FA skeleton (green). A threshold-free cluster enhancement method was applied using a permutation-based inference tool for nonparametric statistics. The number of permutations was 10,000, and the left-right orientation is according to the radiological convention. ACC: anterior cingulate cortex, ACR: anterior corona radiata, L: left, WM: white matter, FA: fractional anisotropy, RD: radial diffusivity.

Table 3. Regions showing significantly positive correlation between the serum uric acid levels and fractional anisotropy in the depression group. Voxels showing significant group differences between the depression and healthy control groups are included

Cluster size (voxels)	Peak coordinates (mm)*	Anatomical locations	p†
208	-25, 30, 14	Anterior corona radiata, left	0.0270
	-20, 35, 9	Frontal lobe WM, left	0.0297
	-16, 33, 15	WM in ACC, left	0.0367

*foci for significant differences are listed (corrected p<0.05), †threshold free cluster enhancement corrected p value. ACC: anterior cingulate cortex, WM: white matter

online-only Data Supplement). The largest cluster in the FA correlation data (208 voxels) was located in the left ACR, left frontal lobe WM, and left ACC WM. For the RD correlation data, the regions in which the largest cluster occurred nearly overlapped. There was no significant correlation between the serum uric acid levels and FA or RD values in the HC group.

Subgroup analyses: first-onset vs. recurrent depression group vs. HC group

According to the subgroup analysis, the FA values were significantly lower (TFCE-corrected p<0.05) in the recurrent depression than in the HC group (Supplementary Figure 3A in the online-only Data Supplement). This tendency was not significant in the first-onset depression group (minimum TFCE-corrected p=0.0889) (Supplementary Figure 4A in the online-only Data Supplement). In addition, the RD values were significantly higher in the recurrent depression than in the HC group (Supplementary Figure 3B in the online-only Data Supplement). This tendency was not significant in the first-onset depression group (minimum TFCE-corrected p=0.0746) (Supplementary Figure 4B in the online-only Data Supplement). No significant difference was observed between the first-onset and recurrent depression groups for either the FA or RD values.

Furthermore, we found a trend for elevated MD values in the recurrent depression compared with the HC group (minimum TFCE-corrected p=0.0904). Otherwise, there were no significant differences.

DISCUSSION

Neuroimaging studies in patients with depression have demonstrated alterations in the WM. Here, we report, for the first time, a significant correlation between serum uric acid levels and WM connectivity in patients with MDD. We also provide confirmation for the alterations in the WM integrity in patients with MDD compared with HCs. These observations are in agreement with previous reports on the reduced FA values in the body and genu of the corpus callosum,[58-61] left cerebral peduncle,[58] bilateral frontal lobe WM,[61-68] bilateral SCR,[58] bilateral ACR,[60] bilateral ACC WM,[59,68,69] anterior and posterior limbs of the left internal capsule,[58,70,71] left PTR,[60,72] bilateral SLF,[71,73-75] left SFO,[76] and left external capsule.[58] Therefore, in this study, we focused on regions that showed positive correlations between the FA values and serum uric acid levels in patients with MDD, namely the left ACR, left frontal lobe WM, left ACC WM.

The FA values are indicative of WM integrity.[77,78] Thus, reduced FA values reflect a reduction in fiber density or WM abnormalities. As patients with MDD have lower uric acid levels[22,24] and decreased FA values,[35] a positive correlation is possible between these two factors.

Previous studies have reported the effects of uric acid, particularly in Alzheimer's disease, mild cognitive impairment,[79] and Parkinson's disease,[80] focusing on its neuroprotective role against the IO&NS pathway. The WM is known to be more vulnerable to oxidative stress than the GM[29] because of its lower blood flow[81] and the accelerated destruction of demyelinated axons[81] but also because of the high sensitivity of its components, i.e., axons and oligodendrocytes, to oxidative stress.[30] In this perspective, it is possible to postulate that uric acid prevents the impairment of WM connectivity, seen in depression, by blocking WM alterations, which could explain the positive correlation between its serum levels and FA values in our study. Furthermore, the related brain regions might constitute the locations at which the brain-protective effects of uric acid occur.

Elevations in the RD values are known to be associated with demyelination or dysmyelination.[82] Thus, it can be presumed that alterations in WM regions, seen in our results, namely the decreased FA and increased RD values, are caused by myelination deficits. If this is the case, then demyelination might be that deficit because the reduced uric acid levels could render the affected brain regions more susceptible to oxidative stress. The results from the subgroup analysis, according to which the reduced FA and elevated RD values were more prominent in the recurrent than in the first-onset depression group, further support possible demyelination rather than dysmyelination deficits. This is because the higher incidence of oxidative stress in the recurrent depression group may have led to a greater degree of WM destruction than in the case of the first-onset depression group.

The altered brain areas, which correlated with the uric acid levels, were found along the left frontal lobe WM and the left ACC WM, as the left ACR belongs to these areas. These areas are known to be affected by oxidative stress. Evidence of increased oxidative stress in the frontal lobe of patients with depression has been reported[83,84] and shown to be related to the disease symptoms.[85] Therefore, decreased FA values in these areas can be, at least partially, explained by the increased oxidative stress in the case of reduced uric acid levels.

One of the affected regions in our study was the frontal lobe, which is linked to executive functions, including learning, planning, remote memory activation, and responses to environmental stimuli.[86] The frontal lobe is also related to cognitive function, inhibition, and personality. Thus, lesions in this area can result in dysexecution, disinhibition, and apathy.[86] These symptoms are reflected by impaired reasoning, inability to maintain attention, disorganized behavior, memory impairment, and personality changes. Contrastingly, the frontal lobe is also known to be related to late-life depression,[61,63,64,68] depression in young adults,[62] severity of depression symptoms,[65] and rumination.[67] Thus, our results are in agreement with these associations.

Our results indicate the ACC, which is critical for mood regulation, as another prominent brain area in depression. As the ACC mediates motivated behavior, lesions in this region cause psychomotor retardation, including apathy and lack of initiative,[87] observed in patients with depression. Clinically, there are reports associating the right ACC with late-life depression[68] and WM alterations lateral to the cingulate gyrus with poor outcomes.[64] The present outcome is in accordance with previous studies, indicating a relation between the ACC and depression.[59,68,69]

The study has several limitations. First, the sample size in each group was relatively small for uric acid comparisons, although it was large enough for the DTI imaging study. Second, the eTIV was significantly smaller in the depression group than in the HC group. Although we excluded the effect of this difference using ANCOVA, using eTIV as well as age and sex as covariates, there might still be a slight bias in our results. Because an eTIV difference is possibly itself a characteristic of depression,[88] such a difference in our results could be normal. Third, a causal relationship cannot be conclusively drawn. Fourth, the smoking status of the study participants was not thoroughly assessed; therefore, it was not included as a covariate. Smoking has been reported to affect the microstructural integrity of WM,[89] but its potential impact on our results is uncertain.

In conclusion, the present study is the first to demonstrate an association between altered WM connectivity and serum uric acid levels in patients with MDD. Our findings suggested that uric acid plays a crucial role in the pathophysiology of depression in association with WM alterations. Further studies will be needed to unveil the exact mechanisms.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2017.12.17.

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