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Correlations between COMT polymorphism and brain structure and cognition in elderly subjects

An observational study

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Abstract

The catechol-O-methyltransferase (COMT) gene has been noted to play an important role in individual variations in the aging process. We investigated whether COMT polymorphism could influence cognition related to white matter networks. More specifically, we examined whether methionine (Met) allele loading is associated with better individual cognitive performance. Thirty-four healthy elderly participants were recruited; each participant's COMT genotype was determined, and Korean version of Montreal Cognitive Assessment scores and a diffusion tensor image were obtained for all participants. The Met carrier group showed significantly lower mean diffusivity, axial diffusivity, and radial diffusivity values for the right hippocampus, thalamus, uncinate fasciculus, and left caudate nucleus than the valine homozygote group. The Met carrier group also scored higher for executive function and attention on the Korean version of Montreal Cognitive Assessment. Based on these results, we can assume that the COMT Met allele has a protective effect on cognitive decline contributing to individual differences in cognitive function in late life period.

Abbreviations: AD = axial diffusivity, CN = caudate nucleus, COMT = catechol-O-methyltransferase, DA = dopamine, DLPFC = dorsolateral prefrontal cortex, DNA = Deoxyribonucleic Acid, DTI = diffusion tensor image, FA = fractional anisotropy, FSL = FMRIB Software Library, HC = hippocampus, IFOF = inferior fronto-occipital fasciculus, MCI = mild cognitive impairment, MD = mean diffusivity, Met = methionine, MMSE = mini-mental status examination, MoCA-K = Korean version of Montreal Cognitive Assessment, MRI = magnetic resonance imaging, PFC = prefrontal cortex, RD = radial diffusivity, ROIs = region of interests, TE = echo time, TM = thalamus, TR = repetition time, UF = uncinate fasciculus, Val = valine, VLPFC = ventrolateral prefrontal cortex.

Keywords: cognition, COMT, diffusion tensor image, dopamine, elderly, polymorphism

1. Introduction

Cognitive decline can be observed in all humans as they age.[1] It affects all cognitive functions, including memory, attention, and executive function,[2] which involve large areas of the frontotemporal and subcortical networks.[3] Since function is strongly related to structural integrity, cognitive decline, even that normally associated with aging, is expected to cause a decrease in the volume of related brain areas.[4] As the degree of age-related decline can vary significantly across individuals, structural variation in elderly is a topic of great interest in aging studies.[5]

Cognition could be influenced by various genetic polymorphisms. Among these, catechol-O-methyltransferase (COMT) gene has received much attention.[6–8] In the single nucleotide polymorphism of the COMT gene, valine (Val) is replaced by methionine (Met) at the codon 158 on chromosome 22q11. This substitution decreases enzymatic activity in Met homozygotes 4-fold, reducing the amount of frontal dopamine (DA) degradation, resulting in greater DA availability at the

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receptors.[9] DA availability decreases exponentially in older populations in an inverted U curve.[6] However, individuals who are more strongly influenced by COMT genetic polymorphism (such as senile subjects) show greater variability between groups with different Met allele loads.[4,10]

Recent advances in diffusion tensor image (DTI) techniques have facilitated the investigation of white matter structural integrity based on the characteristics of water diffusion. When DTI is combined with an examination of cognitive functions, a relationship between changes in microstructural integrity and cognitive decline may be observed.[11] In addition, previous studies have shown that DA influences myelination in healthy subjects; there is an extensive pattern of negative correlations between cortical and subcortical gray matter DA D2/D3 receptor density and white matter fractional anisotropy (FA).[12] Animal studies also suggest that DA plays a developmental role on oligodendrocyte in the formation of myelin.[13] Therefore, the impact of COMT gene polymorphism on cognitive decline could be clinically significant.

In this study, we aimed to determine the effect of COMT polymorphism on white matter integrity in older adults. We hypothesized that COMT polymorphism in terms of Met allele loading could differently influence cognition-related white matter networks and the Met allele may be associated with better cognitive performance.

2. Materials and methods

2.1. Subjects

Thirty-four healthy elderly participants (M:F = 23:11; mean age: 70.24 ± 7.18 years; range: 53-82) were recruited. Some of the findings related to the effects of COMT polymorphism on repeated transcranial magnetic stimulation have already been published elsewhere.[14] The inclusion criteria were as follows. All subjects were over 50 years old; scored at least 24 on the mini-mental status examination (MMSE); were able to perform daily activities independently without any subjective cognition problems; showed no abnormalities on an magnetic resonance imaging (MRI) other than white matter hyper-intensities or an incidental small lacunar lesion (≤5 mm diameter); had no conditions affecting brain structure or function (e.g., stroke, diabetes, head trauma, or depression) and were not using any cognitively active medications.

All participants provided written informed consent to their participation in this study. The study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (IRB number.2013-I063). During the first visit, participants were genotyped, took a MMSE, and received an MRI. They took the Korean version of Montreal Cognitive Assessment (MoCA-K)[15] during the second visit. All participants took the MMSE; however, 12 participants refused to take the MoCA-K (5 Val/Met, 7 Val/Val) because they did not want to undergo a precise cognitive assessment.

2.2. Magnetic resonance imaging

All MRI measurements were conducted using a whole-body clinical 3.0 T MRI scanner (Philips Intera, Amsterdam, The Netherlands). High-resolution T1-weighted imaging was acquired using multi shot turbo field echo pulse sequence [repetition time = 9.3 ms; echo time = 4.6 ms; flip angle = 80; field of view = 230 × 230 mm, slice thickness = 1 mm, 160 slices]. DTI was acquired using a diffusion-weighted echo planar imaging sequence (repetition time = 5,000 ms; echo time =100 ms; slice thickness = 2.2 mm; no gap; in-plane resolution = 2.4 × 2.4 mm, 45 independent diffusion gradient directions using b = 1,000 s/mm^2). DTI data were analyzed using FMRIB's Diffusion Toolbox from the FMRIB Software Library (FSL). DTI data was preprocessed using eddy current artifacts correction and motion artifact correction based on 3D rigid-body motions. Non-brain tissue was removed using the brain extraction tool implemented in the FSL package. DTI data were calculated for each voxel after fitting the diffusion tensor model obtained from the resulting diffusion tensor eigenvalues (×λ1, λ2, λ3), which capture the length of the longest and shortest axis of the ellipsoid in each voxel. FA, a measure of the degree of diffusion anisotropy, was calculated from the standard formula:

$$FA = \sqrt{\frac{3}{2}}\frac{\sqrt{\lambda_1 - <\lambda>)^2 + (\lambda_2 - <\lambda>)^2 + (\lambda_3 - <\lambda>)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \in [0, 1]$$

Mean diffusivity (MD), a measure of the amount of diffusion calculated by average value of λ1, λ2, and λ3 ((λ1 + λ2 + λ3)/3). Axial diffusivity (AD) was defined as the largest eigenvalue (λ1), which captures the longitudinal diffusivity, whereas radial diffusivity (RD) was defined as the shortest axis of the ellipsoid perpendicular to λ1 (λ2 + λ3)/2). Then, mean FA values were extracted from the region of interests (ROIs). In order to get DTI parameters from each ROI of the whole brain, we used 2 Atlases; International Consortium Brain Mapping-DTI-81, which contains various axonal tracts with different trajectories (i.e., corticospinal tract, medial lemniscus, corona radiata, etc) and the Automated Anatomical Atlas,[16] using the FSL meants command.

2.3. Genotyping

All participants underwent a venous blood sample for genotype analysis. Deoxyribonucleic Acid (DNA) extraction was performed from ethylenediaminetetraacetic acid- blood samples of all probands according to standard protocols. Ethical approval for genotyping was provided by the ethics committee of the Hallym University. Genomic DNA extracted from peripheral lymphoblasts was used for sequencing. To examine polymorphisms of the COMT gene (rs4680), polymerase chain reaction and Sanger sequencing of exon 4 in COMT were done. Briefly, the reaction mixture contained 1 μL of gDNA of 50 ng, 3 μL of 10× polymerase chain reaction buffer, 3 μL of 2.5 mM dNTP, 1 μL of forward primer (5'-GGGCCTACTGTGGCTA CTCA-3'), 1 μL of reverse primer (5'-GTGGTCGAGGAAGACCATGT-3'), and 0.2 μL of Taq polymerase that was added to water (total volume, 30 μL). All samples were amplified at 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 45 seconds for 30 cycles and sequenced using an ABI 3730 sequencer.

When performing analyses, we grouped the participants according to Met dominance model (Met carrier group; including Met/Met and Val/Met participants, Val homozygote group; including Val/Val participants). This model was chosen based on previous study showing best efficiency of Met dominance model for highlighting genotype effects on cerebral activity.[17]

2.4. Cognitive function test

The cognitive function was assessed using the Korean version of the MoCA-K,[15] a screening test more sensitive to detect mild cognitive impairment and Alzheimer disease. We adapted the MoCA-K because its' sensitivity in detecting mild cognitive impairment (MCI) is excellent (90%), and is useful for the mild stages of cognitive impairment.[18] In this study, we used a cut off score of MoCA-K to 23 or below for screening MCI. Because past studies demonstrated that using cut off score of 26 or below showed good sensitivity but fair specificity, falsely identified normal individuals as MCI, who scored between 24 and 26. Also reducing the cut off score to 23 or below optimized both sensitivity and specificity to 96% and 95%, respectively for detecting MCI.[19,20]

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 24.0 software (IBM, Armonk, NY). The normality of the data was demonstrated by Kolmogorov-Smirnov goodness-of-fit test. To compare the difference between 2 groups of COMT polymorphisms, we used independent *t* test. To evaluate the association of the specific gene allele on cognitive function, we used Fisher exact test. Pearson correlation analysis was done to verify the relationship between changes of diffusion metrics of ROIs and age decline. To determine whether structures differing diffusion metrics according to genetic polymorphism were affected by aging, we also investigated the relationship between aging and genetic polymorphism by performing Pearson correlation respectively in 2 subgroups (Val homozygote, Met carrier) in each. Statistical significance was defined as a P value of $<.05$.

3. Results

3.1. Participant characteristics

The participants' characteristics are shown in Table 1. Fourteen participants were Val homozygotes, and 20 participants were Met carriers (5 Met/Met participants and 15 Val/Met participants). The average age in the Val homozygote group was 72.5 ± 5.7 years; in the Met carrier group, the average age was 68.7 ± 7.8 years. The age of all participants as well as the age of each group followed normal distribution (Supplemental appendix S1, http://links.lww.com/MD/G702). There were no statistically significant differences in the ages of the 2 groups ($P=.126$). In the Val homozygote group, 9 subjects were females and 5 were male; there were 14 females and 6 males in the Met carrier group. There were also no significant differences in gender composition between the 2 groups ($P=.808$). MMSE scores did not differ significantly between the groups ($P=.808$). Only 7 Val homozygote and 15 Met carrier participants took the MoCA-K during the second visit, so we analyzed the MoCA-K scores of this subgroup. There were no significant differences between the 2 groups ($P=.108$), nor were there significant differences in genotype or age between those who took the MoCA-K and those who dropped out. Although the diffusion metrics showed a significant difference in the FA of the right red nuclei and the AD of the left inferior cerebellar peduncles of the 2 groups, this finding was not relevant to our key result.

Table 1

Participant characteristics.

	Val homozygote N = 14	Met carrier N = 20	Statistic
Age (yrs)	72.5 (5.7)	68.7 (7.8)	0.126*
Gender	9F/5M	14F/6M	0.808†
MMSE	26.2 (1.8)	26.9 (2.3)	0.520*
Complete study (N)	7	15	
MoCA-K	19.4 (5.1)	22.9 (4.9)	0.108*

Data are expressed as mean (standard deviation).

Met = methionine, MMSE = mini-mental status examination, MoCA-K = Korean version of Montreal Cognitive Assessment, N = number, Val = valine.

* Independent *t* test.

3.2. Group differences in diffusion metrics

The diffusion metrics data of each structure were all normally distributed. The Met carrier showed significantly lower MD (mean [standard error]; Met carrier, 1.11 [0.15]; Val homozygote, 1.24 [0.17], $P=.02$), AD (Met carrier, 1.39 [0.17]; Val homozygote, 1.53 [0.19], $P=.03$) and RD (Met carrier, 0.96 [0.15]; Val homozygote, 1.10 [0.17], $P=.01$) values for right hippocampus (HC) than the Val homozygote. The Met carrier showed significantly lower MD (MET carrier, 1.48 [0.22]; Val homozygote, 1.65 [0.22], $P=.04$), AD (Met carrier, 1.82 [0.21]; Val homozygote, 1.98 [0.20], $P=.04$) and RD (Met carrier, 1.32 [0.22]; Val homozygote, 1.49 [0.12], $P=.04$) values for right thalamus than the Val homozygote. The Met carrier showed significantly lower MD (Met carrier, 0.85 [0.06]; Val homozygote, 0.92 [0.11], $P=.04$), AD (Met carrier, 1.20 [0.07]; Val homozygote, 1.28 [0.11], $P=.02$) and RD (Met carrier, 0.68 [0.06]; Val homozygote, 0.73 [0.12], $P=.04$) values for right uncinate fasciculus (UF) than the Val homozygote. The Met carrier showed significantly lower MD (Met carrier, 1.63 [0.35]; Val homozygote, 1.86 [0.33], $P=.04$), AD (Met carrier, 1.87 [0.32]; Val homozygote, 2.10 [0.30], $P=.04$) and RD (Met carrier, 1.50 [0.36]; Val homozygote, 1.75 [0.35], $P=.04$) values for left caudate nucleus (CN) than the Val homozygote (Fig. 1).

3.3. Relationship between cognitive function and COMT polymorphism

When the participants were classified as normal or subnormal based on the MoCA-K cut-off score of 23, the Met carrier group showed a significantly higher percentage of normal function than the Val homozygote group (normal/below normal: Met carrier 6/9, Val homozygote 6/1, $P=.04$) (Fig. 2). Furthermore, when the subscales of MoCA-K scores were compared, the Met carrier group showed significantly higher executive function and attention scores than the Val homozygote group (Table 2). However, there was no significant correlation between diffusion metrics and cognitive function.

3.4. Age-related decline in brain structure

Regardless of genetic polymorphisms, structures that showed significant age-related degeneration appeared in many regions in DTI. Decreased FA and increased MD, AD, and RD values were observed in both sides of the amygdala and in the hypothalamus, thalamus, fornix, stria terminalis, orbitofrontal cortex, cingulum, nucleus accumbens, CN, corpus callosum, anterior corona radiata, middle cerebellar peduncle, tapetum, right superior

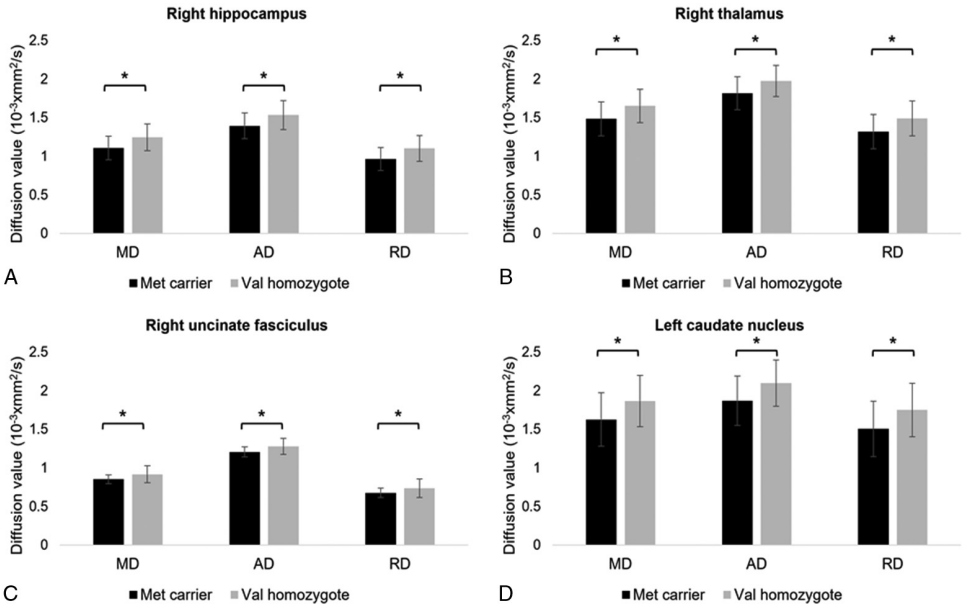

Figure 1. Regions showing difference of diffusivity based on Met dominant model. (A) The Met carrier showed significantly lower MD (mean [standard error]; Met carrier, 1.11 [0.15]; Val homozygote, 1.24 [0.17], $P = .02$), AD (Met carrier, 1.39 [0.17]; Val homozygote, 1.53 [0.19], $P = .03$) and RD (Met carrier, 0.96 [0.15]; Val homozygote, 1.10 [0.17], $P = .01$) values for right hippocampus than the Val homozygote. (B) The Met carrier showed significantly lower MD (Met carrier, 1.48 [0.22]; Val homozygote, 1.65 [0.22], $P = .04$), AD (Met carrier, 1.82 [0.21]; Val homozygote, 1.98 [0.20], $P = .04$) and RD (Met carrier, 1.32 [0.22]; Val homozygote, 1.49 [0.12], $P = .04$) values for right thalamus than the Val homozygote. (C) The Met carrier showed significantly lower MD (Met carrier, 0.85 [0.06]; Val homozygote, 0.92 [0.11], $P = .04$), AD (Met carrier, 1.20 [0.07]; Val homozygote, 1.28 [0.11], $P = .02$) and RD (Met carrier, 0.68 [0.06]; Val homozygote, 0.73 [0.12], $P = .04$) values for right uncinate fasciculus than the Val homozygote. (D) The Met carrier showed significantly lower MD (Met carrier, 1.63 [0.35]; Val homozygote, 1.86 [0.33], $P = .04$), AD (Met carrier, 1.87 [0.32]; Val homozygote, 2.10 [0.30], $P = .04$) and RD (Met carrier, 1.50 [0.36]; Val homozygote, 1.75 [0.35], $P = .04$) values for left caudate nucleus than the Val homozygote. AD = axial diffusivity, MD = mean diffusivity, Met = methionine, RD = radial diffusivity, Val = valine. $^{*}P < .05$ for independent t test.

fronto-occipital fasciculus, right pars triangularis, left angular gyrus, and the left sagittal stratum inferior fronto-occipital fasciculus (IFOF). To determine the age correlation patterns in the 2 groups, we further analyzed correlations in ROIs that showed a significant difference in diffusion metrics. In the Val homozygote group, age correlated significantly with degeneration in the FA (Pearson correlation coefficient, r = –0.714, $P < .01$), MD (r = 0.664, $P = .01$), AD (r = 0.646, $P = .01$), and RD (r = 0.671, $P < .01$) of the left CN; in the FA (r = –0.619, $P = .02$), MD (r = 0.589, $P = .03$), and AD (r = 0.586, $P = .03$) of the right TM; and in the RD (r = 0.550, $P = .04$) of the right HC and the MD (r = 0.586, $P = .03$) of the right UF. However, in the Met carrier group, age correlated significantly with degeneration in the MD (r = 0.467, $P = .04$) and AD (r = 0.477, $P = .03$) of the right TM and in the RD (r = 0.450, $P = .04$) of the right HC (Fig. 3). Therefore, the diffusion metrics in the TM and HC correlate with age in both groups, whereas the CN and UF correlate with age only in the Val homozygote group.

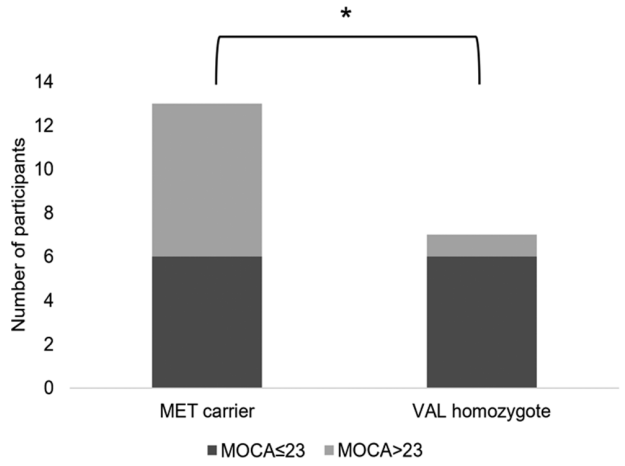

Figure 2. Composition of Montreal Cognitive Assessment scores according to genotype. Met carrier group showed a significantly higher percentage of normal cognition function than the Val homozygote group ($P = .04$). Met = methionine, Val = valine. $^{*}P < .05$ for Fisher exact test.

4. Discussion

In this study, we found better cognitive function in the domain of attention and executive function in the Met carrier group of

Table 2

Subscore of MoCA-K score.

	Met carrier	Val homozygote	*P* value
Measure (perfect score)			
Visuospatial (3)	2.58 ± 0.99	1.86 ± 1.34	.19
Executive function (2)	1.25 ± 0.87	0.43 ± 0.79	.05*
Attention (6)	5.50 ± 0.67	3.57 ± 0.23	.01*
Language (6)	4.67 ± 1.43	5.00 ± 0.57	.56
Abstract reasoning (2)	1.33 ± 0.88	1.28 ± 0.95	.91
Memory (5)	1.50 ± 1.73	1.42 ± 1.81	.93
Orientation (6)	5.91 ± 0.28	6.00 ± 0.00	.46

Met = methionine, Val = valine.
* $P < .05$ for independent t test.

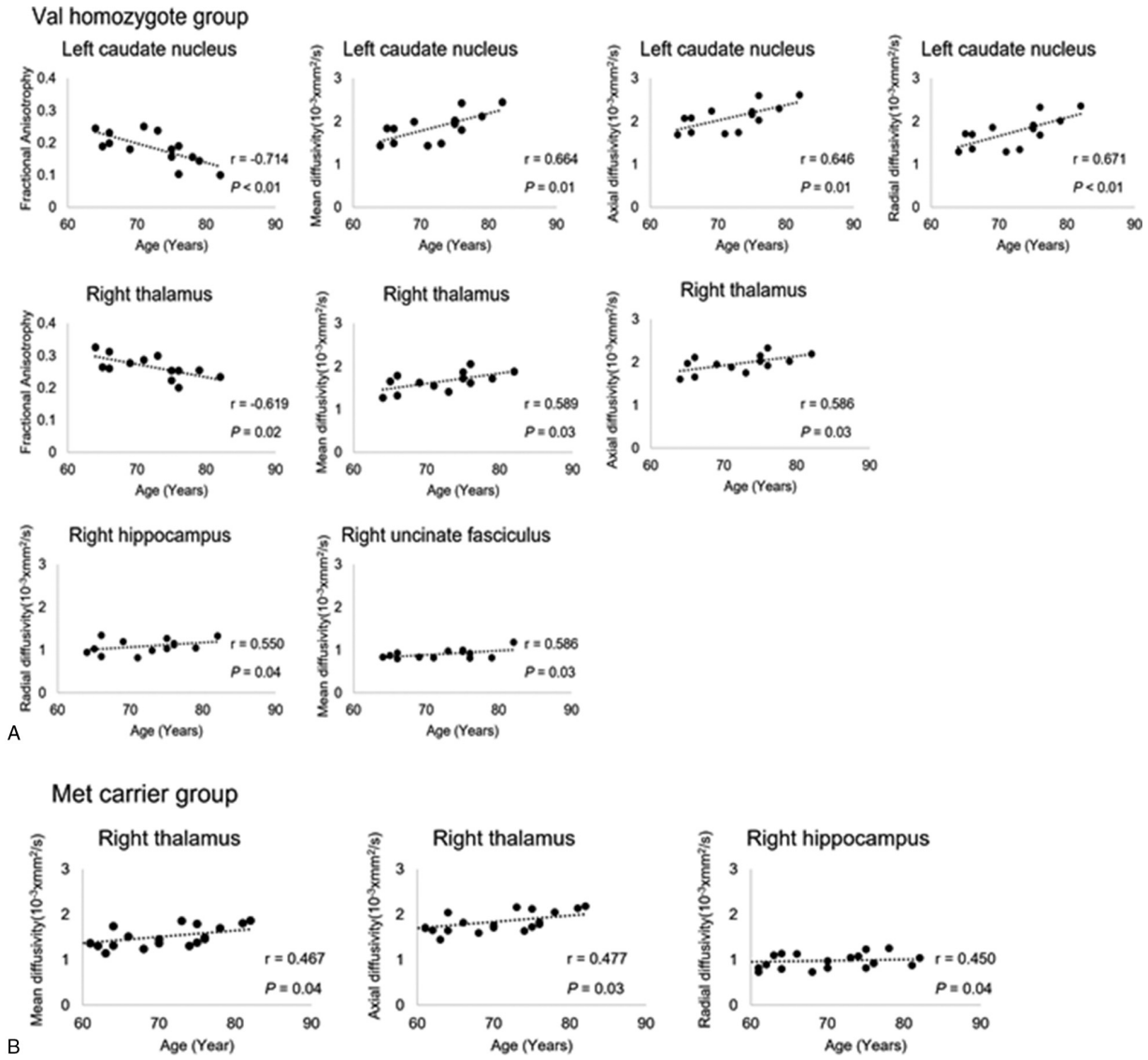

Figure 3. Relationship between age and diffusion metrics of brain structures in each genotype. (A) In the Val homozygote group, the FA of the left CN was lower with age, MD, AD, and RD of the left CN were higher with age. Also, the FA of right TM was lower with age, MD and AD of the right TM were higher with age. The RD of the right HC and the MD of the right UF were higher with age. (B) In the Met carrier group, the AD and RD of the right TM were higher with age and the RD of the right HC was higher with age. AD = axial diffusivity, CN = caudate nucleus, FA = fractional anisotrophy, HC = hippocampus, MD = mean diffusivity, Met = methionine, RD = radial diffusivity, TM = thalamus, Val = valine.

COMT polymorphism. The diffusion values showed significantly lower in the CN, HC, TM, and UF in the Met carrier group, which area encompassing the ventrolateral prefrontal cortex (VLPFC), temporal lobe and subcortical structure. Among them, there was no age effect in CN and UF in the Met carrier group, which suggests that those structure may have influenced by the difference in DA release induced by COMT polymorphism. The clinical implication of this finding would be that Val homozygotes type would have to cope with possible cognitive vulnerability in late period of life due to the decreased DA efficiency.

The effect of COMT polymorphism on brain function has been investigated widely.[21] Many studies have shown that the Met allele is related to better cognitive function,[7] including working memory, executive function,[22–25] reward anticipation,[26] processing speed, and episodic memory.[27] Some negative effects have also been reported, including increased pain sensitivity,[28–30] increased sensitivity to unpleasant emotions and anxiety,[31,32] and decreased ability to switch tasks.[33] It is noteworthy that these effects were measured mostly based on function while subjects performed a dynamic task. The main neural system of working memory is the dorsolateral prefrontal cortex (DLPFC), and most studies using functional tasks have demonstrated increased activity (reduced efficiency) in the DLPFC in Val homozygotes. This could be caused by decreased DA input due to the increased DA turnover by the COMT.

In contrast to the relatively large body of evidence on cognitive performance, structural differences in the brain have received little attention.[34–41] Previous studies have found that the total volume of frontal gray and white matter,[42] the density of regional gray matter,[38] and the volume of the controls measured using deformation-based volumetry[35,37] do not differ significantly by COMT genotype. However, these negative

results are not surprising as all of these studies used younger subjects. Since the effect of DA on cognition is a nonlinear, dose-sensitive inverted U-shape,[6] the effect of COMT genotype may be maximized in elderly subjects, and make them vulnerable to genetic effects. Studies that included middle-aged and/or older subjects have found significantly decreased volume in the HC,[40,43] in the HC with temporal lobe,[39] and in the diffusion metrics in the portion of cingulum that extends to the HC.[34] Few studies have reported structural differences correlating with COMT polymorphism in healthy, very old subjects, and only 1 study has reported a relationship between white matter integrity and cognition in old age (60-87 years).[44] Papenberg study examined the 7 major tracts that pass through the prefrontal cortex (PFC) and reported that the Met homozygote group had significantly better white matter integrity in the cingulate gyrus, superior longitudinal fasciculus, forceps minor, and IFOF.[44] Aside from the differences in our study's ROIs (in addition to the major white matter tracts, we examined various cortical white matter and subcortical gray matter structures) and some differences in grouping (Met homozygotes vs Val allele in the previous study), the findings of above are quite different from us, as we found reduced integrity of CN and UF in Val homozygotes group compared to Met carriers. However, when they analyzed the data after stratifying the subjects into 2 age groups instead of 3, they did observe an association between white matter microstructure and perceptual speed in the oldest age group. This is in line with Laukka et al[45] and demonstrates the significance of IFOF, which fiber traverses ventrolateral part of PFC overlapping UF.

Our important findings are the differences in the diffusion metrics of the CN and the UF that correlate with genotype. The CN is part of the striatum; it is consistently active when expectations about feedback are violated and plays a role in reward-mediated learning.[46] This function can be processed through integration with the PFC by updating and maintaining information in the working memory.[47,48] Therefore, efficiency of the working memory could be significantly modulated by the neurotransmitter DA.[49,50]

The D1 receptor is involved in stabilizing information in the working memory against distraction in the PFC and D2 receptors. It is more abundant in the striatum and is involved in updating information by marking salience, predicting errors,[51,52] and training working memory tasks such as letter memory.[53] In the present study, these overarching mechanisms in the striatum could have influenced diffusion metrics in the Met allele by increasing the efficiency of DA signaling, leading to better executive function. Increased attention might also be related to the enhanced DA efficiency in the CN associated with the Met allele due to an increased signal-to-noise ratio during novel tasks.

Interestingly, we observed no significant changes in DLPFC white matter integrity, whereas the diffusion metrics of the CN differed significantly by genotype. One plausible explanation for this is differences in the development and activation of the striatum and the PFC in adolescence and early adulthood. DA transporter levels in the striatum increase in late childhood, before PFC maturation, which occurs throughout adolescence.[54,55] Increased striatal activation coupled with decreased PFC activation in adolescence[56–58] might have led to this difference in the present study. Furthermore, considering the putative inverted U-shaped dose-response curve for the effects of DA, the increased DA level in the Met allele might be higher than optimal, which could result in better cognitive function in the Val group during adolescence with the opposite effect on the structure.[59,60]

The UF is a white matter tract that connects the VLPFC to the anterior temporal lobe, which is involved in memory, language, and social emotional processing.[61] One of the fronto-striatal circuits is the connection from the VLPFC to the ventromedial caudate. The ventromedial caudate plays a critical role in relative reward processing, such as the ability to delay gratification.[62,63] We assume that these patterns of behavior might be characteristics of the Met allele and might cause the increased integrity of the UF; this possibility warrants further study.

Previous studies on the effect of COMT polymorphism on structural changes in the brain have reported changes to the HC in middle-aged and older subjects.[22,39,40,42] When we divided our subjects into 3 groups by Met allele load (Met/Met, Val/Met, and Val/Val) and analyzed our data, only the right precuneus showed significant structural differences (see Supplemental appendix S2, http://links.lww.com/MD/G703). The precuneus is densely connected to the HC, which, along with the TM, is an important functional network for episodic and autobiographical memory.[64] Our findings demonstrate that the HC, the precuneus, and the TM differ in COMT polymorphism. However, those ROIs are well correlated with age in both the Met allele and the Val homozygote. Clearly, these ROIs are affected by age, although there are significant differences in their diffusion metrics.

This study has some limitations. First, in this study, the white matter was divided according to major white matter tracts, which lowers the information power, as 1 white matter fiber affects a large region of the brain regardless of individual cognitive function. As we thought it would be much easier to conceptualize the relationship between structure and function, we examined ROIs by tract and white matter by cortical parcellation using DTI. Second, although we recruited healthy elderly participants, the mean MoCA score of all participants was 21, which is below normal. We assumed that, as our participants were quite old, some degree of cognitive impairment was normal. Third, we only assessed cognitive function through a simple MoCA test; we were not able to investigate cognitive decline in detail. Finally, the distribution of COMT polymorphism in our sample was not even; only 15% of our subjects were Met/Met group. However, this distribution is consistent with the average proportion of COMT polymorphism in the Korean population.

Based on these results, we can assume that the COMT Met allele has a protective effect on age-related degeneration by increasing DA levels. It could be a major contributing factor to individual differences in cognitive decline. Further study is needed to assess these findings in more detail.

Supplementary materials: Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G685, Figure S2, Supplemental Digital Content, http://links.lww.com/MD/G686.

Author contributions

WKY designed the experimental protocol. WKY, HJA recruited the patients. HJA, EC, WK performed the assessments. EC, HJA analyzed and wrote the manuscript. WKY, SHO, KIJ revised the manuscript. All authors read and approved the final manuscript.

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