White matter integrity in alcohol-dependent patients with long-term abstinence

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Abstract

Based on association studies on amounts of alcohol consumed and cortical and subcortical structural shrinkage, we investigated the effect of chronic alcohol consumption on white matter pathways using probabilistic tractography.

Twenty-three alcohol-dependent men (with an average sobriety of 13.1 months) from a mental health hospital and 22 age-matched male healthy social drinkers underwent 3T magnetic resonance imaging. Eighteen major white matter pathways were reconstructed using the TRActs Constrained by UnderLying Anatomy tool (provided by the FreeSurfer). The hippocampal volumes were estimated using an automated procedure. The lifetime drinking history interview, Alcohol Use Disorder Identification Test, Brief Michigan Alcoholism Screening Test, and pack-years of smoking were also evaluated.

Analysis of covariance controlling for age, cigarette smoking, total motion index indicated that there was no definite difference of diffusion parameters between the 2 groups after multiple comparison correction. As hippocampal volume decreased, the fractional anisotropy of the right cingulum-angular bundle decreased. Additionally, the axial diffusivity of right cingulum-angular bundle was positively correlated with the alcohol abstinence period.

The results imply resilience of white matter in patients with alcohol dependence. Additional longitudinal studies with multimodal methods and neuropsychological tests may improve our findings of the changes in white matter pathways in patients with alcohol dependence.

Abbreviations: AD = axial diffusivity, AUDIT-K = Korean version of the Alcohol Use Disorder Identification Test, CAB = cingulum-angular bundle, CCG = cingulum-cingulate gyrus endings, DTI = diffusion tensor imaging, eTIV = estimated total intracranial volume, FA = fractional anisotropy, FDR = false discovery rate, MAST = Michigan Alcoholism Screening Test, MD = mean diffusivity, MRI = magnetic resonance imaging, RD = radial diffusivity, SLFP = superior longitudinal fasciculus-parietal endings, TMI = total motion index, TRACTULA = TRActs Constrained By Underlying Anatomy.

Keywords: alcohol dependence, cingulum angular bundle, diffusion tensor imaging, white matter pathway

1. Introduction

In 2018, according to the World Health Organization, the global prevalence of alcohol dependence was 2.6%, respectively. The adverse effects of alcohol on the brain vary according to the amount and duration of consumption.[1–12] Alcohol consumption affects the brain structure; with increasing alcohol consumption, an inverse U- or J-shaped association with brain damage is observed.[3] Moreover, regardless of alcohol abuse during adolescence, the initiation of alcohol consumption itself affects the brain’s structures.[4] Several studies have reported that alcohol-dependent subjects have a reduced volume of cortical-subcortical structures and enlarged ventricles.[5–7] These structural changes are accompanied by an impairment in the memory formation, decision-making ability, emotional and cognitive network impairments.[8,9]

A postmortem study reported that the reduction of the white matter volume in alcohol-dependent patients is associated with maximal daily alcohol consumption.[10,11] The white matter largely consists of lipid-rich myelinated oligodendrocytes, which are wrapped around the neuronal axons and mediate efficient nerve conduction. A spectrometric study found that lipid expression is inhibited in the white matter of alcohol-dependent patients.[12] Advances in magnetic resonance imaging (MRI) have enabled the noninvasive detection of microstructural changes in the brain. Diffusion tensor imaging (DTI) is a sensitive method for determining white matter integrity; it utilizes the translational motion of the water molecules present in the brain tissue,[13–15]; as the myelination of the neurons progresses, the anisotropy of these water molecules increases, which can be detected on DTI as an increase in the fractional anisotropy (FA). Changes in diffusion parameters, such as the axial, radial, and mean diffusivities (AD,
RD, and MD, respectively), along with a decrease in the FA, indicate neuronal damage (such as demyelination) secondary to normal aging or clinical disease. Studies which utilized multimodalities such as histology and DTI have suggested that a decreased AD and increased RD represent the loss of the myelinated axon; FA may have a lesser sensitivity for detection of and discrimination between axonal loss and demyelinated axon.\[^{16,17}\] RD changes could affect the AD, due to the effect of the crossing fiber, which is perpendicular to the main fiber.\[^{18}\] Severe demyelination is observed as the RD increases; as the myelin repair progresses, the RD decreases.\[^{19,20}\]

Thus far, DTI studies have revealed that white matter pathways that are associated with interhemispheric connections or episodic and visuospatial working memory are disrupted in patients with alcohol dependence.\[^{21-28}\] Disrupted white matter integrity in the corpus callosum or other regions, including the cingulum, was associated with an impaired neuropsychological performance, with effects observed in decision-making, executive function, and memory.\[^{22,23,25}\] Furthermore, frontal white matter disruption is dependent on the amount of alcohol consumption.\[^{29}\] However, there are inconsistent results on whether long-term sobriety normalizes white matter disruptions such as lowered axonal density or demyelination. Sorg et al reported that there were no significant differences in the white matter integrity between alcohol-dependent patients on abstinence for more than 6 months and a control group.\[^{30}\] Studies with an average abstinence period of 2 years demonstrated no significant differences in the FA, but higher AD and RD\[^{31}\] or a lower FA in several regions.\[^{32}\]

In this study, we aimed to investigate the differences in the integrity of white matter pathways between alcohol-dependent patients, who at the time of the study were in long-term alcohol abstinence, and age-matched normal controls, by controlling for confounding factors such as the age, head motion during image acquisition, and cigarette smoking.\[^{24,33}\] For investigating white matter pathway integrity, we used the FA, AD, RD, and MD values estimated by TRActs Constrained by Underlying Anatomy (TRACULA), a global probabilistic tractography tool. We also aimed to investigate the associations between white matter integrity and the alcohol abstinent period, cigarette smoking, and hippocampal volume which is commonly reduced in alcohol-dependent patients.

2. Methods

2.1. Participants

The participants with alcohol dependence were recruited from the inpatient department of a mental health hospital specialized in the management of alcohol use disorder, and were categorized into the alcohol group. All participants in alcohol group were abstained from alcohol. The healthy participants of the control group were recruited through advertisements in the community. All participants in the alcohol group met the criteria for alcohol dependence, whereas those in the control group did not. All participants were right-handed and were interviewed by a psychiatrist using the Structured Clinical Interview of Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Participants were excluded if they had history of substance abuse except nicotine; history of head trauma; major psychiatric disorders such as schizophrenia and the bipolar disorder; and structural abnormalities of the brain, as visualized on MRI. The Korean versions of the Alcohol Use Disorder Identification Test (AUDIT-K), the Brief Michigan Alcoholism Screening Test (MAST), the lifetime drinking history interview, and the pack years of smoking were assessed for all participants. Our data on current and past drinking history were collected based on participant’s self-reports and available medical records. The study protocol was approved by the Institutional Review Board of the Chungbuk National University, Cheongju, Republic of Korea (2014-0002-11). All participants provided an informed consent.

2.2. Magnetic resonance image acquisition

Structural images of the brain were collected using the 3T Achieva MRI scanner (Philips Medical Systems, Best, Netherlands) at the Ochang Campus of the Korea Basic Science Institute in Cheongju, Republic of Korea. All subjects underwent scanning with the same 32-channel head coil and the same pulse sequence. The parameters for rapid acquisition gradient echo sequence were obtained using following protocol; Repetition Time = 6.8 ms, Echo Time = 3.1 ms, Field Of View = 256 mm, flip angle = 9°, voxel size = 1.0 × 1.0 × 1.2 mm, and 170 slices without gaps. The parameters for diffusion-weighted imaging were as follows: voxel size = 2.0 × 2.0 × 3.0 mm, TE = 70 ms, TR = 6332 ms, number of volumes = 34, Bandwidth = 2725.2 Hz/pixel, and b-value = 1000 s/mm².

2.3. Image analysis

On the basis of the sagittal T1-weighted images, subcortical segmentation and cortical parcellation were processed using the FreeSurfer software package (version 5.3.0; https://surfer.nmr.mgh.harvard.edu). The details of the overall processes are described elsewhere.\[^{34–36}\] Briefly, nonbrain tissue was removed by a hybrid watershed algorithm. Thereafter, automated Talairach transformation was performed and the subcortical white and deep grey matter were segmented. The sum of the bilateral hippocampal volumes was normalized using total intracranial volume before comparing between groups. The normalized volume was derived using the following formula, which provides an advantage over other methods such as the proportion method.\[^{37–39}\]

\[
\text{Volume}_{\text{adj}} = \text{Volume}_{\text{nat}} - b(\text{eTIV}_{\text{nat}} - \text{mean eTIV}_{\text{nat}})
\]

Where \(\text{Volume}_{\text{adj}}\) is the corrected hippocampal volume, \(\text{Volume}_{\text{nat}}\) is the hippocampal volume in the native space, and \(b\) is the slope of the volume regression on the estimated total intracranial volume (eTIV). Mean eTIV is the sample mean of the eTIV. All total hippocampal volumes reported in the results section are the \(\text{Volume}_{\text{adj}}\).

The diffusion-weighted images were processed using TRACULA within the FreeSurfer software package. TRACULA is an automated tool for anatomically reconstructing the major white matter pathways through global probabilistic tractography method using previously generated anatomical data obtained from processing T1-weighted MRI scans. It reconstructs the known connection between 2 end regions by utilizing previously reported information on the anatomy of the pathways from a set of training subjects; it has proven useful in diseased populations.\[^{40}\] Before reconstruction, the diffusion-weighted images were corrected for Eddy-currents to mitigate the distortions caused by large diffusion gradients. Thereafter, the processed images were registered with the MNI 152 database template.
Next, TRACULA used the ball-and-stick model available with the bedpostx tool of the Functional MRI of the Brain Software Library software to estimate the probability distribution of each parameter at every voxel. We reconstructed the following 18 major white matter pathways with mean diffusion parameters of FA, AD, RD, and MD: the corpus callosum-forceps major, corpus callosum-forceps minor, bilateral anterior thalamic radiations, cingulum-angular bundle (CAB), cingulum-cingulate gyrus endings (CCG), corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus-parietal endings (SLFP), superior longitudinal fasciculus-temporal endings, and uncinate fasciculus (Fig. 1). For quality assessment, head motion measurements were considered, because head motion can alter the intensities of the diffusion-weighted images. The total motion index (TMI) was used for head motion quality control during image acquisition, as described previously.\textsuperscript{[40,41]} We also set TMI as a nuisance variable in group comparisons of diffusion parameters to confirm that the confounding effect of motion was eliminated.\textsuperscript{[33]}

### 2.4. Statistical analysis

Statistical analyses were performed using the CRAN R statistical package, version 3.6.0. Initially, the demographic variables and eTIV, TMI, and hippocampal volume were analyzed using the 2-sample \( t \)-test or the Mann–Whitney test depending on normality and uniformity. Because age, smoking, and TMI are known to be potential nuisances to diffusion parameters,\textsuperscript{[33,41,42]} we conducted an analysis of covariance setting group as the predictor and age, TMI, and pack-years of smoking as the covariates on each.

![Figure 1. Visualization of probability distributions of white matter pathways. ATR = anterior thalamic radiations, CAB = cingulum-angular bundle, CCG = cingulum-cingulate gyrus endings, CST = corticospinal tract, FMAJOR = corpus callosum-forceps major, FMINOR = corpus callosum-forceps minor, ILF = inferior longitudinal fasciculus, SLFP = superior longitudinal fasciculus-parietal endings, SLFT = superior longitudinal fasciculus-temporal endings, UNC = uncinate fasciculus.](image-url)
diffusion parameter of the white matter pathways. The level of statistical significance was corrected using false discovery rate (FDR) of q-value < 0.05 within each diffusion parameter as in previous study. [13] To investigate the associations between white matter pathway disruption and hippocampal atrophy which is commonly observed in alcohol-dependent patients, correlations between diffusion parameters and the hippocampal volume were tested using the Spearman correlation test. Further exploratory analysis was performed to assess the effects of the abstinent periods from alcohol and pack-years of smoking on white matter integrity using analysis of covariance and the Spearman correlation test.

3. Results

3.1. Demographic characteristics and hippocampal volume

The analysis of neuroimaging data was performed in 23 patients in the alcohol group and 22 subjects in the control group. Table 1 shows the demographic characteristics of the 2 groups. There were no significant between-group differences in the age or year of education and pack years of smoking was higher in alcohol group (u = 2.44, P = .015).

An evaluation of the lifetime history of alcohol consumption revealed that patients in the alcohol group consumed significantly more alcohol than participants in the control group (u = 3.82, P = .0001). The mean period of sobriety in the alcohol group was 13.1 ± 16.9 months. The mean AUDIT-K (t = 6.56, P = 5.53E–08) and brief MAST (u = 5.52, P = 3.31E–08) scores were significantly higher in the alcohol group than in the control group. The control group subjects were social drinkers with an AUDIT-K score of 28.5 ± 5.52 and brief MAST score of 2.1 ± 0.70.

Abstinent period (mo) 13.1 ± 16.9
Total alcohol consumption 16,360 ± 3329
Alcohol consumption in last 5 yr 16,962 ± 3705

The sum of the bilateral hippocampal volume was significantly lower in the alcohol group than in the control group (t = –3.61, P = .0008).

3.2. Between-group comparisons of diffusion parameters

Based on analysis of covariance controlling for age, pack years of smoking, and TMI, there was no significant effect of group in all diffusion parameters of 18 major white matter pathways (Table 2, see also Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A172). Using a less conservative threshold without FDR correction, group effect was present in FA, AD, RD of right SLFP, and MD of corpus callosum-forceps major.

3.3. Associations with the hippocampal volume

In the alcohol group, hippocampal volume was significantly associated with FA and RD of the right CCG (FA: r = 0.700, corrected P = .004; RD: r = –0.673, corrected P = .008). Weak

Analysis of covariance on each white matter pathways. Age, pack years of smoking, and TMI were covariates. q adjusted P-value using FDR correction. η² effect size. Bold: significant at P < .05 (uncorrected). AD = axial diffusivity, ATR = anterior thalamic radiations, CAB = cingulum-angular bundle, CCG = cingulum-cingulate gyrus endings, CST = corticospinal tract, FA = fractional anisotropy, FMAJOR = fasciculus-major endings, SLFT = superior longitudinal fasciculus-temporal endings, UNC = uncinate fasciculus.
associations were observed with FA and RD of left SLFP (FA: cor=0.574, corrected \(P = .037\), RD: cor=−0.560, corrected \(P = .049\)), AD of right bilateral anterior thalamic radiations (cor=−0.590, corrected \(P = .027\)), inferior longitudinal fasciculus (cor=0.555, corrected \(P = .027\)), SLFP (cor=−0.560, corrected \(P = .027\)) and UNC (cor=−0.570, corrected \(P = .027\)). FA and RD of left CAB showed trends of an association; however, these associations were not significant after FDR correction (see Table S2, Supplemental Digital Content, for whole outcomes, http://links.lww.com/MD2/A173). From the partial correlation analysis adjusting effects of age, pack-years of smoking, and TMI also revealed significant correlation between FA (cor=0.602, uncorrected \(P = .005\)), RD (cor=−0.584, uncorrected \(P = .007\)) of the right CAB and hippocampal volume (see Table S2, Supplemental Digital Content, http://links.lww.com/MD2/A173 and Table S3, Supplemental Digital Content for whole outcomes, http://links.lww.com/MD2/A174).

3.4. Associations with clinical variables within each group

An abstinence period from alcohol and AD of right CAB showed a positive association in the partial correlation test with age, pack-years of smoking, and TMI as nuisance variables (cor=0.509, uncorrected \(P = .022\)). In analysis of covariance for investigation of the effect of cigarette smoking on diffusion parameters, there was no significant effect in the 2 groups after multiple comparison correction. However, exploratory analysis revealed that partial correlation coefficient between FA (cor=−0.486, uncorrected \(P = .035\)), RD (cor=0.515, uncorrected \(P = .024\)) of right CCG, RD of right SLFP (cor=0.570, uncorrected \(P = .011\)) and pack-years of smoking were significant in alcohol group (see Table S4, Supplemental Digital Content, http://links.lww.com/MD2/A175, Table S5, Supplemental Digital Content, http://links.lww.com/MD2/A176, and Table S6, Supplemental Digital Content for whole outcomes, http://links.lww.com/MD2/A177).

4. Discussion

Participants in the alcohol group in our study were middle aged men who were admitted to inpatient mental health hospitals, with abstinence from alcohol for an average of 13.1 months. On the contrary, all participants in the control group were social drinkers. Thus, our participants represent patients with alcohol dependence who are currently in recovery as well as social drinkers.

In previous studies, nontreatment-seeking alcohol-dependent individuals presented with a disrupted white matter integrity that was inversely related with the amount of alcohol consumption.\(^{[24]}\) Patients with alcohol dependence in short-term sobriety also presented with a disrupted white matter integrity, commonly in the corpus callosum or the cingulum.\(^{[22,23,25]}\) However, studies on long-term alcohol abstinence in alcohol-dependent patients have inconsistent findings regarding white matter disruption. In case of at least 6 months of sobriety, higher AD and RD were widely observed; however, there were no significant differences in the FA compared with healthy population.\(^{[31]}\) Studies with larger samples have also reported no differences in the FA between the alcohol-dependent and control groups.\(^{[30]}\) Conversely, I study reported that subjects who are sober for an average of 5 years had a reduced FA throughout the frontal, superior white matter.\(^{[43]}\) Another study with an abstinence period from 0.1 to 28 years also reported a lower FA, mostly in the right hemisphere including the cingulum and the superior longitudinal fasciculus.\(^{[26]}\)

Such inconsistencies regarding white matter integrity in alcohol-dependent patients on long-term abstinence could be attributed to heterogeneous treatment and detoxification programs, which result in varying degrees of disrupted white matter recovery. Demyelinated white matter due to binge alcohol use is partially reversible with sobriety alone.\(^{[44]}\) The white matter of alcohol-dependent patients who participated in rehabilitation programs did not differ from that of the control group; relapsed patients had a disrupted integrity, implying resilience of the white matter.\(^{[30]}\) The alcohol group in our study included treatment-seeking patients who had abstained from alcohol for at least 3 months and were undergoing medical treatment and rehabilitation. Therefore, relatively preserved integrity in white matter pathways in our study, are in line with reports from previous studies and could be suggestive of an appropriate treatment effect and sobriety.\(^{[30,31]}\)

Notably, the FA and AD of the right SLFP in the alcohol group were greater than those of the control group, whereas the RD was lower than that of the control group using a less conservative threshold without FDR correction, suggesting that those in the alcohol group had a greater axonal density. A study on alcohol use disorder in young individuals also reported an increased FA in the superior longitudinal fasciculus and regional associations with the default mode, dorsal attention, and somatomotor network.\(^{[43]}\) Previous studies in our laboratory have confirmed that the alcohol group showed a decreased resting-state intranetwork connectivity, especially in the cingulo-opercular task control network.\(^{[46]}\) The prefrontal cortex, dorsal anterior cingulate, and parietal cortex in the control network are connected through a part of the superior longitudinal fasciculus and the cingulum bundle\(^{[47–50]}\); the control network is known to be associated with cognitive functions such as decision making, working memory, and task switching,\(^{[51–53]}\) all of which are frequently deteriorated in alcohol-dependent patients.\(^{[9]}\) Our results suggest functional correlates of altered axonal density and disrupted connectivity in regions involved with cognitive control in the alcohol group. For example, subjects with cognitive decline due to a neurodegenerative disease show an increased axonal density, implying compensation for functional deterioration.\(^{[54]}\)

The hippocampus is a subcortical structure with cell proliferation, and is vulnerable to toxicity or neurodegeneration. Our laboratory had previously confirmed that the volume of the hippocampal subfields is decreased in alcohol-dependent patients.\(^{[5]}\) In the present DTI analysis, the integrity of the bilateral CAB was positively correlated with the hippocampal volume. The modality utilized in our study divided the cingulum into 2 separate segments; an upper segment along the cingulate gyrus (CCG) and a lower segment along the ventral part of the hippocampus (CAB).\(^{[40,41]}\) Cognitive functions associated with the cingulum can be distinguished depending upon its subdivision. Various studies have revealed that the FA of the CCG is associated with a better executive function.\(^{[35–60]}\) The FA of the CAB is similarly associated with better episodic memory either independently\(^{[61]}\) or with the hippocampal or fornix volume.\(^{[62–64]}\) The cingulum microstructure is correlated with episodic memory in mild cognitive impairment\(^{[57,58]}\) and Alzheimer’s disease.\(^{[65,66]}\) In patients with alcohol dependence, the disrupted integrity and functional activation of the left posterior cingulum was associated with a poor visuomotor integration\(^{[21]}\) and the abnormal white matter integrity of clusters including the bilateral
posterior cingulum was associated with an impaired decision making. Therefore, the integrity of cingulum was disrupted in alcohol dependence left-sided,
right-sided bilateral[21]. In most studies, such disruption was observed to be confined to the posterior cingulum; however, disrupted integrity of the superior portion was also reported.68 In line with previous studies, our results suggest that a disrupted CAB is associated with hippocampal shrinkage in alcohol-dependent patients on long-term abstinence.

Additionally, substance-abuse, including the chronic use of cannabis, cocaine, or nicotine, also alters the white matter microstructure.69,70 In a voxel-based analysis of a healthy population, cigarette smoking was associated with a disrupted integrity of the corpus callosum71–73 and the severity of nicotine-dependence was negatively associated with the FA in regions including the cingulum.42 In patients with alcohol dependence under sobriety, microstructural and volumetric recovery were associated with the cessation of cigarette smoking.74,75 All subjects in our study were current smokers and in the alcohol group, the integrity of the right CCG was negatively correlated with pack-years of smoking, implying the effect of smoking on the affected population and the potential positive effect of smoking cessation.

Our study has the following limitations. First, patients in the alcohol group maintained abstinence from alcohol undergoing adequate medical treatment. Thus, our results should be limited to patients with alcohol dependence recovering from the nutritional deficits and toxic effects of chronic alcohol use. Second, for the 8 participants in the control group, the lifetime drinking history of last 5 years before study participation was more than 1000 drinks, suggesting harmful use of alcohol and could be considered to have been exposed to the toxic effect of alcohol. Third, we did not evaluate the neuropsychological test for visuospatial, episodic memory, or language function, which may have deteriorated in the alcohol group. Thus, there was no information on the association between white matter pathways and its function.

Our study investigated that there exists no definite difference in integrity of major white matter pathways reconstructed via probabilistic tractography of patients with alcohol dependence who are abstinence average 13.1 months. We also observed the negative effect of cigarette smoking on white matter and associations with disrupted integrity of right CAB and hippocampalatrophy.

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References
[1] Ding J, Eigenbrodt ML, Mosley TH, et al. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults. Stroke J Am Heart Assoc 2004;35:16–21.
[2] Mukamal KJ, Jr, Longstreth WT, Mittleman MA, Crum RM, Sicovick DS. Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults. Stroke 2001;32:1939–46.
[3] McEvoy LF, Fennema-Notestine C, Elman JA, et al. Alcohol intake and brain white matter in middle aged men: Macroscopic and macroscopic differences. NeuroimageClin 2018;18:390–8.
[4] Luciana M, Collins PF, Muetzel RL, Lim KO. Effects of alcohol use initiation on brain structure in typically developing adolescents. Am J Drug Alcohol Abus 2013;39:345–55.
[5] Lee J, Im S-J, Lee S-G, et al. Volume of hippocampal subfields in patients with alcohol dependence. Psychiatry Res Neuroimaging 2016;258:16–22.
[6] Bühler M, Mann K. Alcohol and the human brain: a systematic review of different neuroimaging methods. Alcohol Clin Exp Res 2011;35:1771–8.
[7] Durazzo TC, Tosun D, Buckley S, et al. Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: relationships to relapse and extended abstinence. Alcohol Clin Exp Res 2011;35:1187–200.
[8] Berre A-PL, Rauchs G, Joie RL, et al. Impaired decision-making and brain shrinkage in alcoholism. Eur Psychiat 2014;29:125–33.
[9] Fama R, Berre A-PL, Sassoon SA, et al. Relations between cognitive and motor deficits and regional brain volumes in individuals with alcoholism. Brain Struct Funt 2019;224:2087–101.
[10] Kri JJ, Halliday GM, Svoboda MD, Cartwright H. The cerebral cortex is damaged in chronic alcoholics. Neurosciene 1997;79:983–98.
[11] de la Monte SM. Disproportionate atrophy of cerebral white matter in chronic alcoholics. Arch Neurol 1988;45:990–2.
[12] de la Monte SM, Kay J, Yalcin EB, Kri JJ, Sheedy D, Sutherland GT. Imaging mass spectrometry of frontal white matter lipid changes in human alcoholics. Alcohol 2018;67:51–63.
[13] Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do’s and don’ts of diffusion MRI. Neuroimage 2013;73:239–54.
[14] Bihan DL. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 2003;4:469–80.
[15] Zahr NM, Pfefferbaum A. Alcohol’s effects on the brain: neuroimaging results in humans and animal models. Alcohol Res Curr Rev 2017;38:183–206.
[16] Tyszka JM, Readhead C, Bearer EL, Pautler RG, Jacobs RE. Statistical diffusion tensor histology reveals regional dysmyelination effects in the shiverer mouse mutant. Neuroimage 2006;29:1058–65.
[17] Boretić S, Escher A, Dallenga T, et al. Assessment of lesion pathology in a new animal model of MS by multiparametric MRI and DTI. Neuroimage 2011;59:2678–88.
[18] Wheeler-Kingshott CAM, Cercignani M. “About axial" and "radial" diffusivities. Magnet Reson Med 2009;61:1255–60.
[19] Song S-K, Yoshino J, Le TQ, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroscience 2005;26:132–40.
[20] Harssan LA, Poulet P, Guignard B, et al. Brain dysmyelination and recovery assessment by noninvasive in vivo diffusion tensor magnetic resonance imaging. J Neurosci Res 2006;83:392–402.
[21] Schulte T, Muller-Oehring EM, Rohlfing T, Pfefferbaum A, Sullivan EV. White matter fiber degradation attenuates hemispheric asymmetry when integrating visuomotor information. J Neurosci 2010;30:12168–78.
[22] Trivedi R, Bagga D, Bhattacharya D, et al. White matter damage is associated with memory decline in chronic alcoholics: a quantitative diffusion tensor tractography study. Behav Brain Res 2013;250:192–8.
[23] Zorlu N, Gelal F, Kuserli A, et al. Abnormal white matter integrity and volume of the brain reward system in alcohol dependence. Psychiatry Res Neuroimaging 2016;258:16–22.

Writing – review & editing: Siekyeong Kim.
[25] Konrad A, Vucurevic G, Lorscheider M, et al. Broad disruption of brain white matter microstructure and relationship with neuropsychological performance in male patients with severe alcohol dependence. Alcohol Alcohol 2012;47:118–26.

[26] Harris GJ, Jaffin SK, Hodge SM, et al. Frontal white matter and cingulum diffusion tensor imaging deficits in alcoholism. Alcohol Clin Exp Res 2012;36:2232–41.

[27] Herting MM, Schwartz D, Mitchell SH, Nagel BJ. Delay discounting behavior and white matter microstructure abnormalities in youth with a family history of alcoholism. Alcohol Clin Exp Res 2010;34:1590–602.

[28] Hill SY, Terveriliger R, McDermott M. White matter microstructure, alcohol exposure, and familial risk for alcohol dependence. Psychiatry Res Neuroimaging 2013;212:43–53.

[29] Sorg SF, Squeglia LM, Taylor MJ, Alhasoon OM, Delano-Wood LM, Grant I. Effects of aging on frontal white matter microstructure in alcohol use disorder and associations with processing speed. J Stud Alcohol Drugs 2015;76:296–306.

[30] Sorg SF, Taylor MJ, Alhasoon OM, et al. Frontal white matter integrity predictors of adult alcohol treatment outcome. Biol Psychiat 2012;71:262–8.

[31] Zorlu N, Ucman TK, Gelal F, et al. Abnormal white matter integrity in long-term abstinent alcohol dependent patients. Psychiay Res Neuroimaging 2014;224:42–8.

[32] Pandey AK, Ardekani BA, Kamarajan C, et al. Lower prefrontal and cingulum bundle fractional anisotropy in young adults with alcohol use disorder. Alcohol Clin Exp Res 2018;42:1883–96.

[33] Pfuhl G, King JA, Gesler D, et al. Preserved white matter microstructure in young patients with anorexia nervosa? Hum Brain Mapp 2016;37:4069–83.

[34] Fischl B, van der Kouvwe A, Destrieux C, et al. Automatically parcelling the human cerebral cortex. Cereb Cortex 2004;14:11–22.

[35] Fischl B, Salat DH, Busa E, et al. Whole brain segmentation automated labeling of neuroanatomical structures in the human brain. Neuroimage 2002;33:341–55.

[36] Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci 2000;97:10505–10.

[37] Buckner RL, Head D, Parker J, et al. A unified approach for morphometric and functional data analysis in young, old, and demmented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage 2004;23:724–38.

[38] Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Correction for head size in brain-imaging measurements. Psychiay Res Neuroimaging 1993;50:391–9.

[39] Sanfilipo MP, Benedict RH, Zivadinov R, Bakshi R. Correction for intracranial volume in analysis of whole brain atrophy in multiple sclerosis: the proportion vs. residual method. Neuroimage 2004;22:1732–43.

[40] Yendiki A, Panneck P, Srivinasan P, et al. Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. Front Neuroimform 2011;5:23.

[41] Yendiki A, Koldewyn K, Kukanouri S, Kanwisher N, Fischl B. Spurious group differences due to head motion in a diffusion MRI study. Neuroimage 2014;88:79–90.

[42] Haldins M, O’Neill J, Tobias MC, Bartzokis G, London ED. Cigarette smoking and white matter microstructure. Psychopharmacology 2012;221:285–95.

[43] Fortier CB, Lertz JC, Salat DH, et al. Widespread effects of alcohol on white matter microstructure. Alcohol Clin Exp Res 2014;38:2925–33.

[44] Yalcin E, McLean T, Tong M, de la Monte SM. Progressive white matter atrophy with altered lipid profiles is partially reversed by short-term abstinence in an experimental model of alcohol-related neurodegeneration. Alcohol 2017;65:51–62.

[45] Chumin EL, Grocco GG, Dzemidzic M, et al. Alterations in white matter microstructure and connectivity in young adults with alcohol use disorder. Alcohol Clin Exp Res 2019;43:1170–9.

[46] Kim S, Im S, Lee J, Lee SG. Disrupted control network connectivity in abstinent patients with alcohol dependence. Psychiatry Invest 2016;14:325–32.

[47] Seeley WW, Menon V, Schatzberg AF, et al. Dissociative intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349–56.

[48] Meyer L, Cunitz K, Obleser J, Friederici AD. Sentence processing and verbal working memory in a white-matter-disconnection patient. Neuropsychologia 2014;61:190–6.

[49] Friederici AD. The cortical language circuit: from auditory perception to sentence comprehension. Trends Cogn Sci 2012;16:262–6.

[50] Tadayonmedj R, Ajiore O. Brain network dysfunction in late-life depression. J Geriatr Psyhch 2014;27:5–12.

[51] Braver TS, Reynolds JR, Donaldson DI. Neural mechanisms of transient and sustained cognitive control during task switching. Neuron 2003;39:713–26.

[52] Crane EA, Wendelen K, Donohue SE, Bunge SA. Neural evidence for dissociable components of task-switching. Cereb Cortex 2006;16:475–86.

[53] Sakai K, Passingham RE. Prefrontal set activity predicts rule-specific neural processing during subsequent cognitive performance. J Neurosci 2006;26:1218–8.

[54] Benitez A, Jensen JH, Helfpern JA. Axonal density and myelin integrity in cognitive decline: a diffusion kurtosis imaging study. Alzheimer’s Dementia 2013;13:774–86.

[55] Charlton RA, Barrick TR, Lawes IN, Markus HS, Morris RG. White matter pathways associated with working memory in normal aging. Cortex 2010;46:474–89.

[56] Kantarcì K, Senjrm ML, Avula R, et al. Diffusion tensor imaging and cognitive function in older adults with no dementia. Neurology 2011;77:26–34.

[57] Metzler-Badeley C, Hunt S, Jones DK, Leemans A, Aggleton JP, O’Sullivan MJ. Temporal association tracts and the breakdown of episodic memory in mild cognitive impairment. Neurology 2012;79:2233–40.

[58] Metzler-Badeley C, Jones DK, Steventon J, Westacott I, Aggleton JP, O’Sullivan MJ. Cingulum microstructure predicts cognitive control in older age and mild cognitive impairment. J Neurosci 2012;32:17612–9.

[59] Takahashi M, Iwamoto K, Fukatsu H, Nagana S, Isakda T, Ozaki N. White matter microstructure of the cingulum and cerebellar peduncle is related to sustained attention and working memory: a diffusion tensor imaging study. Neurosci Lett 2010;477:72–6.

[60] Chiang H-L, Chen Y-J, Shang C-Y, Tseng WY, Gao SS. Different neural substrates for executive functions in youths with ADHD: a diffusion spectrum imaging tractography study. Psychol Med 2014:46:1225–38.

[61] Ezzati A, Katz MJ, Lipton ML, Zimmerman ME, Lipton RB. Hippocampal volume and cingulum bundle fractional anisotropy are independently associated with verbal memory in older adults. Brain Imaging Behav 2015;10:662–9.

[62] Douet V, Chang L. Fornix as an imaging marker for episodic memory deficits in healthy aging and in various neurological disorders. Front Aging Neurosci 2015;5:343. doi: 10.3389/fnagi.2014.00343.

[63] Metzler-Badeley C, Jones DK, Belaroussi B, Aggleton JP, O’Sullivan MJ. Frontotemporal connections in episodic memory and aging: a diffusion MRI tractography study. J Neurosci 2011;31:13236–45.

[64] Rudebeck SR, Scholz J, Millington R, Rohenkohl G, Johansen-Berg H, Lee AC. Fornix microstructure correlates with reollection but not familiarity memory. J Neurosci 2009;29:14987–92.

[65] Kantarcì K, Murray ME, Schwarz CG, et al. White-matter integrity on DTI and the pathologic staging of Alzheimer’s disease. Neurobiology Aging 2015;36:172–9.

[66] Nakata Y, Sato N, Nemoto K, et al. Diffusion abnormality in the posterior cingulum and hippocampal volume: correlation with disease progression in Alzheimer’s disease. Magn Reson Imaging 2009;27:347–54.

[67] Schulze T, Muller-Oehring EM, Sullivan EV, Pfefferbaum A. Synchrony of corticostralial-midbrain activation enables normal inhibitory control and conflict processing in recovering alcoholics. Biol Psychiat 2012;71:269–78.

[68] Pfefferbaum A, Rosenblum M, Rohling T, Sullivan EV. Degradation of association and projection white matter systems in alcoholism detected with quantitative fiber tracking. Biol Psychiat 2009;65:890–90.

[69] Becker MP, Collins PF, Lim KO, Muetzel RL, Luciana M. Longitudinal changes in white matter microstructure after heavy cannabis use. Dev Cogn Neurosci 2015;16:233–35.

[70] Lane SD, Steinberg JL, Ma L, et al. Diffusion tensor imaging and decision making in cocaine dependence. Plos One 2010;5:e11591.

[71] Lin F, Wu G, Zhu L, Lei H. Heavy smokers show abnormal microstructural integrity in the anterior corpus callosum: a diffusion tensor imaging study with tract-based spatial statistics. Drug Alcohol Depend 2013;129:82–7.
[72] Savjani RR, Velasquez KM, Thompson-Lake DGY, et al. Characterizing white matter changes in cigarette smokers via diffusion tensor imaging. Drug Alcohol Depend 2014;145:134–42.

[73] Umene-Nakano W, Yoshimura R, Kakeda S, et al. Abnormal white matter integrity in the corpus callosum among smokers: tract-based spatial statistics. Plos One 2014;9:e87890.

[74] Gazdzinski S, Durazzo TC, Mon A, Yeh PH, Meyerhoff DJ. Cerebral white matter recovery in abstinent alcoholics—a multimodality magnetic resonance study. Brain 2010;133:1043–53.

[75] Zou Y, Murray DE, Durazzo TC, Schmidt TP, Murray TA, Meyerhoff DJ. Effects of abstinence and chronic cigarette smoking on white matter microstructure in alcohol dependence: diffusion tensor imaging at 4T. Drug Alcohol Depend 2017;175:42–50.