감성과학
제20권 4호, 2017
<연구논문>

pISSN 1226-8593
eISSN 2383-613X
Sci. Emot. Sensib.,
Vol.20, No.4, pp.113-126, 2017
https://doi.org/10.14695/KJSOS.2017.20.4.113

Regional Grey and White Matter Changes in the Brain Reward System Among Patients with Alcohol Dependency

Mi-Sook Park* · Ji-Woo Seok** · Eun-Ye Kim*** · Ji-Hye Noh**** · Jin-Hun Sohn*****†

*Department of Rehabilitation Counseling Psychology, Seoul Hanyoung University
**Department of Counseling Psychology, Honam University
***Department of Education, Chungnam National University
****Bioimaging Research Team, Korea Basic Science Institute
*****Department of Psychology, Brain Research Institute, Chungnam National University

Abstract

The purpose of the study was to find grey matter (GM) and white matter (WM) volume reduction in the brain reward system among patients with alcohol dependency. This study investigated regional GM and WM in chronic alcoholic patients, focusing primarily on the reward system, including principal components of the mesocorticolimbic reward circuit as well as cortical areas with modulating and oversight functions. Sixteen abstinent long-term chronic alcoholic men and demographically matched 16 healthy control men participated in the study. Morphometric analysis was performed on magnetic resonance brain scans using voxel-based morphometry (VBM)-diffeomorphic Anatomical Registration through Exponentiated Liealgebra (DARTEL). We derived GM and WM volumes from total brain and cortical and subcortical reward-related structures. Morphometric analyses that revealed the total volume of GM and WM was reduced and cerebrospinal fluid (CSF) was increased in the alcohol group compared to control group. The pronounced volume reduction in the reward system was observed in the GM and WM of the nucleus accumbens (NAc), GM of the amygdala, GM and WM of the hippocampus, WM of the thalamus, GM and WM of the insula, GM of the dorsolateral prefrontal cortex (DLPFC), GM of the orbitofrontal cortex (OFC), GM of the cingulate cortex (CC), GM and WM of the parahippocampal gyrus in the alcohol group. We identified volume reductions in WM as well as GM of reward system in the patients with alcohol dependency. These structural deficits in the reward system elucidate underlying impairment in the emotional and cognitive processing in alcoholism.

Key words: Grey Matter, White Matter, Volume Reduction, Brain Reward System, Alcohol Dependency

---

※ This work was supported by research funding of 2016 Chungnam National University (2016-1411-01).
† Corresponding author : Jin-Hun Sohn (Department of Psychology, Chungnam National University)
E-mail : jhsohn@cnu.ac.kr
TEL : 042-821-6369
FAX : 042-821-8875

1. Introduction

The alcoholism is very costly to the individual and to society and is associated with serious side effects. A main goal of alcohol research is to understand the neural underpinnings associated with the transition from alcohol use to alcohol dependence. According to the study, particularly the changes of the mesocorticolimbic system contribute to the development of alcohol dependence (Koob, 1999). The mesocorticolimbic system plays a key role in control motivational processes such as arousal, reward, and stress (Bowirrat et al., 2005; Oscar-Berman & Bowirrat, 2005). Principal structures of the mesocorticolimbic reward circuit include amygdala, hippocampus, nucleus accumbens (ventral striatum), and ventral diencephalon (including basal forebrain, ventral tegmentum, and hypothalamus), as well as cortical areas with modulating and oversight functions, such as dorsolateral-prefrontal, orbitofrontal, temporal pole, subcallosal, and cingulate cortices, parahippocampal gyri, and the insula (Heimer & Van Hoesen, 2006; Markris et al., 2008; Oscar-Berman & Bowirrat, 2005). According to Markris et al. (2008), this cortical and subcortical circuit is known as the "extended reward and oversight system" or the "reward network", which control primary reward functions. However, in addition to reward functions, this system is linked to motivation and evaluation, approach and avoidance, impulsivity and inhibition, and reward and punishment. Together with associated cortical centers, this system is important for executive functioning, emotional judgment and responses, decision making, and oversight (Oscar-Berman & Bowirrat, 2005).

Many studies have revealed a widespread pattern of atrophy in the mesocorticolimbic system that contribute to the pathophysiology of alcohol dependence (Agartz et al., 1999; Laakso et al., 2000; Makris et al., 2008; Pfefferbaum et al., 2005; Schneider et al., 2001; Sullivan et al., 1995; Sullivan et al., 2000; Szabo et al., 2004). Makris & colleagues (2008), for the first time, comprehensively assessed the reward network as an interconnected system in its entirety and in its subcomponents and reported the presence of morphometric abnormalities in alcoholic subjects in these grey matter of limbic and paralimbic regions. They also showed that volumetric alterations of the reward network were correlated with memory ability (the score of Wechsler Memory Scale) and drinking history among alcoholics. Makris & colleagues (2008) carried out the volume morphometry such as segmentation and cortical parcellation by using semiautomatic method conducted by an experienced research assistant.

In recent years, voxel-based morphometry (VBM) known as a whole-brain unbiased objective technique has been developed to investigate brain differences in vivo using structural magnetic resonance (MR) images. It has been useful in characterizing subtle changes in brain structure in a variety of diseases associated with neurological and psychiatric dysfunction (Mechelli et al., 2005). The advantages of VBM include greater sensitivity for localizing small scale regional differences in grey or white matter. One major limitation of VBM is that imperfectly registered MR images to a common template can lead to false estimates (Bookstein, 2001). In other words, the limitation is that VBM is sensitive to systematic shape differences attributable to misregistration from the spatial normalization step (Ashburner & Friston, 2001). The introduction of diffeomorphic Anatomical Registration through Exponentiated Liealgebra (DARTEL), based on a more sophisticated registration model (American Diabetes Association, 2009), can be helpful to solve this problem. This algorithm could achieve more precise inter-subject registration of brain images, accomplish accurate realignment of the small inner structure (Yassa & Stark, 2009) and attain the best results (Klein et al., 2009).

In the current study, using VBM technique with DARTEL, we expect to identify the shrinkages of grey matter (GM) and white matter (WM) in the reward network among alcoholics. The previous studies on cerebral volume loss mainly focused on the atrophy of GM. In contrast to this, recent findings revealed evidences that WM atrophy might be a significant biomarker of

a psychiatric disorder (e.g., Szeszko, 2005). According to these studies, regional reduction in GM volumes may result from neuronal loss, whereas the atrophy of cerebral white matter may be caused by severe loss of myelin and axons associated with spongiform changes or tissue rarefaction, numerous of foamy macrophages, and proliferation of gemistocytic astrocytes. With respect to the toxic effects of alcohol (Mechtcheriakov et al., 2007), we hypothesized WM volume in the reward network among alcoholics would be different from that of normal controls. The purpose of this study was to investigate the altered density of GM and WM in the reward network among patients with alcohol dependency. In the study, using a male-only group was expected to promote a gender-sensitive approach to understand alcohol effects on the human brain, because there are known gender disparities, such as biological and psychological differences related to alcohol use, that distinguish males from female drinkers (e.g., gender differences in the metabolism and effects of alcohol).

2. Methods and Materials

2.1. Subjects

Right-handed men volunteered as experiment participants who were enrolled in a mental hospital located in the local area. They were eligible to write and communicate without physical disabilities. They were diagnosed as alcohol dependence by a medical doctor based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Through a clinical interview, volunteers who were suffering from other psychiatric disorders other than alcoholism were excluded from the study. The Alcohol Use Disorders Identification Test (AUDIT) was used to measure the degree of alcohol use and the Korean version of the Alcohol Dependence Scale (ADS) to assess the severity of alcohol dependence. Specifically, 16 alcoholic patients participated in the study, who completed a detoxification phase after hospital admission. Their alcohol use characteristics were examined in the reference to the period of 12 months ago before being admitted to the mental hospital. The 16 healthy men matched for age and education level were recruited as the controls. Characteristics on demographics and alcohol use history of the participants with alcohol and control groups were shown in the Table 1. This study was approved by the Institutional Review Board of the University.

2.2. Magnetic Resonance Imaging (MRI) Acquisition

Image data were acquired using ISOL 3.0T Forte Korea located at the Brain Science Research Center (Korea Advanced Institute of Science and Technology).

Table 1. Characteristics on demographics and alcohol use history of the participants in alcohol and control groups

Items	Control group (n=16) M(SD)	Alcohol group (n=16) M(SD)	*t*
Age (years)	50.16(6.10)	49.83(6.60)	0.15
Educational level	12.38(3.57)	10.67(4.05)	0.61
Family history (%)	0.00	44.40	
Number of drinks (day per week)	1.02(1.55)	4.63(2.25)	-5.38***
Amounts of drinks (drinks per drinking day)	2.86(2.10)	16.25(16.08)	-3.30**
Maximum amount of drinks in a lifetime	8.22(11.26)	29.77(24.21)	-3.26**
AUDIT-K	6.38(5.54)	27.89(9.91)	-7.67***
ADS-K	28.05(5.39)	50.00(12.85)	-6.34***

** $p < .01$, *** $p < .001$. Note. Means (standard deviations) are represented. One drink = 14g ethanol. AUDIT-K Korean version of the Alcohol Use Disorders Identification Test, ADS-K Korean version of the Alcohol Dependence Scale.

For each subject, an anatomical image was obtained using a sagittal three-dimensional gradient-echo T1-weighted sequence (TR and TE = 280 and 14 msec, FOV (field of view) = 240mm×240mm×140mm, number of slices = 35, acquisition matrix 256×256, a slice thickness 4 mm, a flip angle 60°). Herlidou-Meme et al. (2003) have previously performed the study to examine the effect of slice thickness (i.e., 2 mm, 4 mm and 6 mm slices) on the classification separability of each tissue pair. They did not find any significant effect for classification accuracy according to the slice thickness. Also, the larger the slice thickness becomes, the higher the signal to noise ratio is. For that reason, we chose 4 mm slice thickness for the study.

2.3. Voxel-Based Morphometry (VBM) Analysis

At first, brain images were pre-processed using SPM8 software implemented in Matlab Version.7.9 (MathWorks, Natick, Massachusetts). An optimized VBM approach following the Diffeomorphic Anatomical Registration through DARTEL was performed. The VBM-DARTEL preprocessing included the following steps. To identify different tissue types automatically [i.e., grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF)] within the images, the new segmentation option was used in SPM8. Then, the DARTEL approach was applied for registration, normalization, and modulation, leaving the images in DARTEL space (In this approach, a DARTEL template is created based on the deformation fields that are produced by the segmentation procedure). Next, all individual deformation fields are warped (and modulated) to match this template and smoothed for the GM and WM images using an 8 mm, full-width-at-half-maximum (FWHM) Gaussian kernel. Typically, FWHM should be at least twice the size of the voxel (Jones et al., 2005). The pixel size is about 1 mm, but we used 8 mm FWHM Gaussian kernel as considering 4 mm slice thickness to increase the signal-to-noise ratio. In the resulting GM images, each voxel represents an absolute amount of GM volume, equivalent to the GM volume per unit before normalization. The preprocessing step of the VBM by using DARTEL in SPM 8 is shown in the Fig. 1.

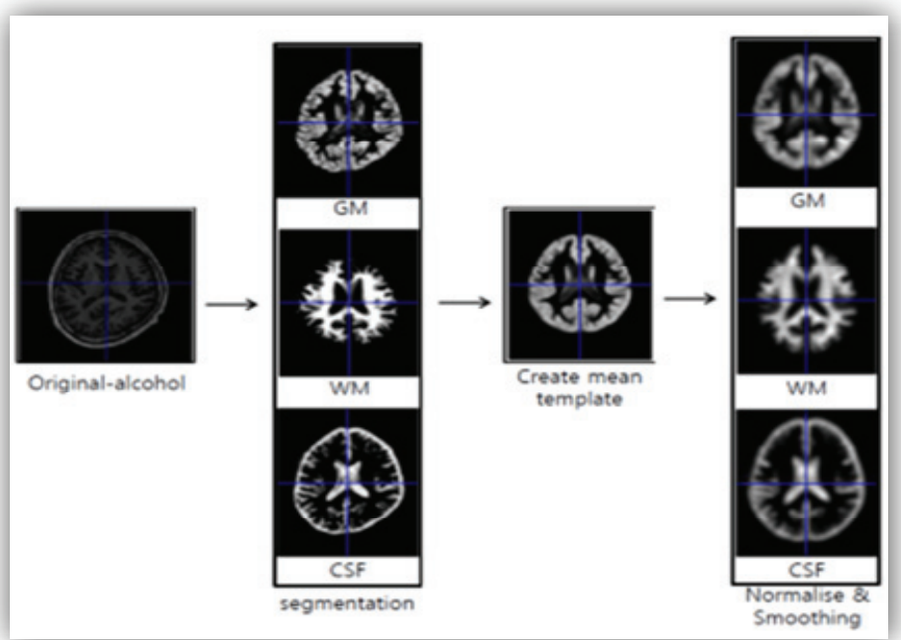

Fig. 1. The preprocessing step of the VBM by using DARTEL in SPM 8

2.4. Region of Interest (ROIs) Analysis

In the 1-st step, statistical analyses were performed with SPM8 using the general linear model based on the Gaussian field theory. The global mean voxel values and the total intracranial volumes (obtained by summing up GM, WM and CSF voxels) were used as confounding covariates in an analysis of covariance to focus on the regional differences in GM. The significance level was set at $p < .05$ false discovery rate (FDR)-corrected for multiple comparisons across the entire brain volume. In the 2-nd step, ROIs in the reward network were based on the study of Makris et al. (2008) and ROIs included in the study were nucleus accumbens (NAc), amygdala, thalamus, hippocampus, cingulate cortex (CC), parahippocampal gyrus, insula, orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (DLPFC). To define the ROIs, WFU-pickatlas 3.0 (Wake Forest University School of Medicine, 2012) was used. By using MATLAB 7.9 script (http: and and www.cs.ucl.ac.uk and staff and g.ridgway and vbm and get_totals.m) (Ridgway et al., 2008), volume from each ROI was extracted and calculated. In order to verify that the difference of brain volume in the ROIs between the groups, independent t-test was conducted by using the SPSS 21. To investigate the association between severity of alcoholism (i.e., AUDIT scores) and brain volume reduction, correlation analysis were also performed by using the SPSS 21.

3. Results

3.1. Whole Brain Analysis

As shown in the Table 2, the total volume of GM (t = -3.53, $p < .001$) and WM ($t = -2.26$, $p < .05$) was reduced and CSF ($t = 4.77$, $p < .001$) was increased in the alcohol group compared to control group. Also, GM and WM of total reward system (sum of all reward volumes for the ROIs) ($t = 3.26$, $p < .01$; $t = 2.05$, $p < .05$) showed a significant decrease in the alcohol group (FDR-corrected, $p < .05$).

3.2. ROI Analysis in the Reward System

Within the reward network, individual structures that demonstrated a significant volumetric reduction were shown in Table 3 and Fig. 2. The structures are specifically, GM and WM of the NAc ($t = -2.191$, $p < .05$; $t = -2.240$, $p < .05$), GM of the amygdala ($t = -3.833$, $p < .01$), GM and WM of the hippocampus ($t = -4.591$, $p < .001$; $t = -3.342$, $p < .01$), WM of the thalamus ($t = -2.599$, $p < .05$), GM and WM of the insula ($t = -3.215$, $p < .01$; $t = -2.112$, $p < .05$), GM of the DLPFC ($t = -2.729$, $p < .05$), GM of the OFC ($t = 2.787$, $p < .01$), GM of the CC ($t = -3.189$, $p < .01$; $t = -2.240$, $p < .05$), and GM and WM of the parahippocampal gyrus ($t = -3.627$, $p < .01$; $t = -3.845$, $p < .01$) (FDR-corrected, $p < .05$). In the correlation results, no relationship was found

Table 2. Morphometric measures of the total extended reward and oversight system (unit: cc)

Regions	Control group (n=16) Mean±SD	alcohol group (n=16) Mean±SD	Group Effect t Value	Cohen's d
Total Cerebral Grey Matter	486.03±60.41	410.42±60.75	-3.53***	1.25
Total Cerebral White Matter	448.98±61.83	402.81±53.62	-2.26*	0.80
Total Cerebrospinal fluid	274.34±41.05	358.01±57.55	4.77***	1.67
Total Reward system (GM)	73.65± 9.19	62.70± 9.82	3.26**	1.15
Total Reward system (WM)	42.44± 6.04	38.27± 5.48	2.05*	0.72

* $p < .05$, ** $p < .01$, *** $p < .001$ Grey Matter is represented as GM; White Matter is represented as WM

Table 3. Volumes of regions within the extended reward and oversight system (unit:cc)

Regions	Control group (n=16) Mean±SD	alcohol group (n=16) Mean±SD	Group Effect *t* Value	Cohen's *d*
Subcortical Reward Regions				
GM of NAc	0.48±0.04	0.44±0.05	-2.191*	0.88
WM of NAc	0.11±0.02	0.10±0.01	-2.240*	0.63
GM of Amygdala	1.75±0.20	1.49±0.18	-3.833**	1.37
WM of Amygdala	0.50±0.07	0.46±0.08	-1.566	0.53
GM of Hippocampus	5.51±0.63	4.56±0.54	-4.591***	1.62
WM of Hippocampus	2.93±0.36	2.54±0.30	-3.342**	1.18
GM of Thalamus	4.49±0.36	4.28±0.59	-1.246	0.43
WM of Thalamus	5.60±0.85	4.89±0.70	-2.599*	0.91
Cortical Reward Regions				
GM of Insula	10.46±1.47	8.87±1.31	-3.215*	1.14
WM of Insula	5.01±0.63	4.57±0.56	-2.112*	0.74
GM of DLPFC	11.69±1.62	10.04±1.79	-2.729*	0.97
WM of DLPFC	5.15±0.82	5.06±0.69	-0.349	0.12
GM of OFC	12.57±1.87	10.59±2.14	-2.787**	0.99
WM of OFC	6.85±1.19	6.18±1.36	-1.489	0.52
GM of Cingulate cortex	20.34±2.73	17.04±3.10	-3.189**	1.13
WM of Cingulate cortex	13.89±1.94	12.55±1.94	-1.951	0.70
GM of Parahippocampal gyrus	6.35±0.82	5.39±0.68	-3.627**	1.28
WM of Parahippocampal gyrus	2.38±0.41	1.93±0.25	-3.845**	1.32

* $p < .05$, ** $p < .01$, *** $p < .001$ Grey Matter is represented as GM; White Matter is represented as WM

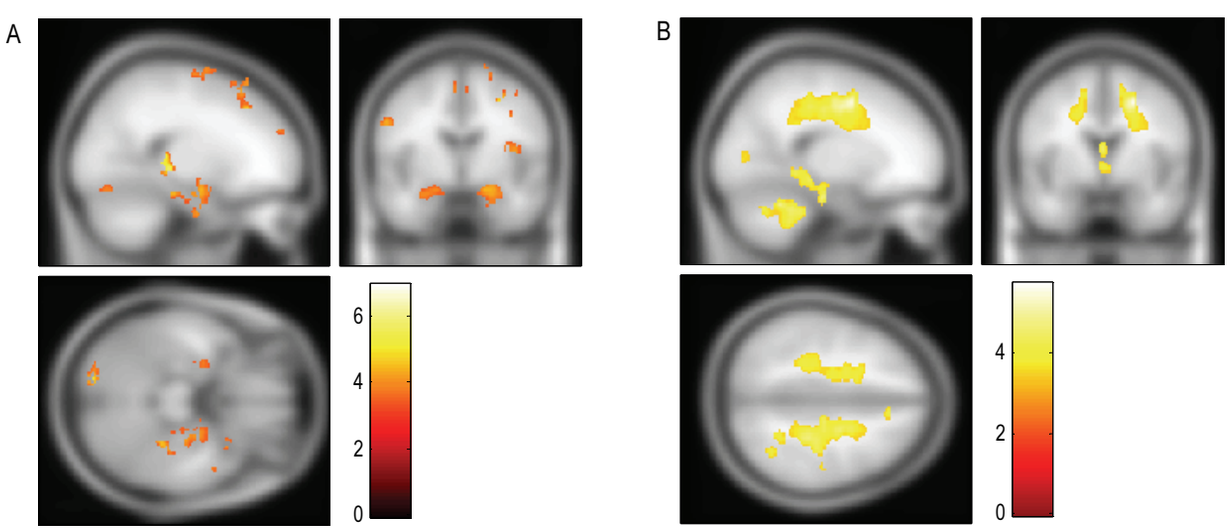

Fig. 2. Areas of significant grey and white matter decrease in patients with alcohol dependency relative to healthy controls. Results are illustrated as statistical parametric map blobs superimposed on the slices of a T1-weighted mean picture in standard stereotactic space from all 32 study participants. Threshold was set at FDR-corrected, $p < .05$. (A) Grey matter (B) White matter

between the degree of alcoholism (i.e., AUDIT score) and total brain volume of GM ($r = 0.18$, $p > .05$), WM ($r = 0.22$, $p > .05$), and CSF ($r = -0.15$, $p > .05$). Similarly, GM and WM of the total reward system or the subregions (i.e, ROIs) were not correlated with the severity of alcoholism at the level of $p < .05$.

4. Discussion

We investigated brain alterations in patients with alcohol dependency using VBM, which allows the analysis of regional GM and WM partitions. Recently, there are studies on the relationship between Fractional anisotropy (FA) using Diffusion Tensor Imaging (DTI) and volumetry measured by T1 imaging. These studies found some significant correlation between them and Hugenschmidt and colleagues (2007) identified FA was more sensitive than volumetry methods. However, DTI obtains only information related to WM, but not that of GM. In the study, we applied VBM method since we would like to identify information both on WM and on GM of brain structure. We tested the hypothesis that brain atrophy is shown in alcoholics, especially in the reward network. In the study, we found that the volume of GM and WM were reduced and CSF was increased in the alcohol group compared to control group. The volume reduction in the specific regions of the reward system includes the GM and WM of the NAc, GM of the amygdala, GM and WM of the hippocampus, WM of the thalamus, GM and WM of the insula, GM of the DLPFC, GM of the OFC, GM of the CC, GM and WM of the parahippocampal gyrus in the alcohol group. Previous structural neuroimaging studies on alcoholism concentrated global atrophic changes in cerebral cortex, white matter, and cerebellum, plus local effects in the hippocampus (Sullivan, 2000), showing volume reduction (Agartz et al., 1999; Laakso et al., 2000, Moselhy et al., 2001; Sullivan et al., 1995). Neuropathologic observations suggested neuronal loss associated with alcoholism in the prefrontal association cortex, hypothalamus, amygdala, and cerebellum (Hill et al, 2001). What is distinguished from the results, the study revealed WM volumetric reduction in the specific reward regions in addition to those of GM. The findings support even low-to-moderate consumption of alcohol was associated with brain atrophy (Ding et al., 2004).

The reward network may be a central part of the neurobiology of drug addiction, alcohol dependence in particular (Koob, 1999). Structural abnormality in this system could increase risk of drug-seeking behaviors (Blum et al., 1996; Bowirrat & Oscar-Berman, 2005). The extended reward and oversight system is made up of a network of cortical and subcortical regions. By virtue of its cortical and subcortical centers and its multiple interconnections (Fuster, 2003; Fuster, 2006), the reward network plays a key role in sensory processing, stimulus-reward associations and memory, and determination of mood (Fuster, 1997; Fuster, 2006). This system is associated with executive functions, decision-making (Nixon & Parsons, 1990), inhibition of perseverative behaviors (Schaefe et al., 2006), and initiating drug and alcohol abuse or relapse (Bowirrat & Oscar-Berman, 2005).

4.1. DLPFC

Regarding the brain volume reduction of DLPFC, our data are in line with the previous findings on the involvement of frontal cortical areas in the brain of patients with alcohol addiction. Numerous neuropsychological studies demonstrated substantial deficits in frontal executive functions in patients with alcohol dependence (Moselhy et al., 2001). There are abundant interconnections between the DLPFC and many reward network structures (LaBar & Cabeza, 2006; Schmahmann & Pandya, 2006) that allows it to

evaluate reward-related information (Heimer & Van Hoesen, 2006). Furthermore, the basal forebrain and NAc structures are strongly interconncected and those are involved in building a relationship between stimulus cues and reward.

4.2. Thalamus

With the frontal reduction, we found the pronounced decrease in WM volumes of the thalamus in our alcohol group. The thalamus serves as a major junctional complex that mediate input to the prefrontal cortex, and it has been suggested that the prefrontal cortex should be defined on the basis of its anatomic relationship with the medial dorsal thalamus (Moselhy et al., 2001). This might reflect that the WM atrophy of thalamus might be related to the reduction of frontal regions and contribute to the damage to the connectivity between the prefrontal and thalamic regions.

4.3. Cingulate Cortex (CC)

Additionally, we found a decrease in the cingulate cortex in the alcoholic group also points to a dysfunctional fronto-limbic system, as the cingulate cortex, especially the anterior cingulate cortex connects to the frontal lobes, albeit indirectly, as well as to the limbic system, in a circuit that is related to emotional processing and drug reward and craving (Grusser et al., 2004; Heimer & Van Hoesen, 2006; Myrick et al., 2004). The OFC is also implicated in the processing of affective stimuli, especially learning associated with emotion. In sum, damage to the frontal regions with CC may be associated with an impairment in relating a reward (i.e., alcohol) to an affective stimulus (Hornak et al., 1996) in alcoholics. There is strong evidence of deficiency in emotional processing in alcoholism that implicates orbitofrontal cortex and and or anterior cingulate cortex (Davis et al., 2005; Kornreich et al., 2001; Uekermann et al., 2005; Volkow et al., 1997).

4.4. Hippocampus and Amygdala

Our results showed alcohol-induced alterations of the GM and WM of the hippocampus. There is a lot of evidence of possible mechanisms underlying the effect of alcohol on the hippocampus. Chronic alcohol intake can greatly boost level of lipofuscin deposition in neurons in the area of the hippocampus. It is known to be ethanol induces the fatty acid ethyl esters in the brain and that appears to particularly damage to the hippocampus. In addition, animal models have demonstrated that excessive drinking of ethanol can produce necrotic neurodegeneration in the brain regions most closely associated with the hippocampus (Obernier et al., 2002). The volume reduction of hippocampus and amygdala indicated that the volumetric decrease in alcoholics was localized in the basolateral nuclear group. Remarkably, connections of amygdala with other structures in the reward network, such as DLPFC, anterior insula, hippocampus, and NAc, are through its basolateral nuclear group. The basolateral nuclear group is believed to be part of the frontotemporal association system mediating outcome-specific incentive processes (Corbit & Balleine, 2005; Swanson, 2003), while the central nucleus is involved in autonomic behavior modulating the general motivational influence of reward-related events. Hippocampal and amygdala volume reductions have been previously reported in alcoholics (Agartz et al., 1999; Beresford et al., 2006; Hill et al., 2001), and reduced amygdala volume was found among adolescents from families with high-risk alcoholism, suggesting a possible neurodevelopmental component (Hill et al., 2001).

4.5. White Matter (WM)

Regarding the relationship between regional brain atrophy and alcohol, it is known that ethanol can increase the release of arachidonic acid from cell membranes and induce oxidative stress in the brain by increased cyclo-oxygenase activity. Furthermore, hydroxyethyl free radicals derived directly from ethanol are nearly as damaging as hydroxyl radicals (Sun et al., 2002). It is also reported from animal studies that alcohol causes cell death as compared with rats fed an alcohol-free diet, rats fed a liquid diet containing moderate amounts of ethanol for 6 weeks had a 66.3% decrease in the number of new neurons and a 227~279% increase in cell death in the dentate gyrus (Herrera et al., 2003). Regarding the WM volume reduction, we could noticeably revealed WM volume reduction in the NAc, hippocampus, thalamus, insula, and parahippocampal gyrus by separating WM from GM in the reward system. It is well known that alcoholism is particularly damaging to cerebral WM, as has been reported by postmortem neuropathology (Pentney, 1991; Putzke et al., 1998; Tarnowska-Dziduszko et al., 1995) and by in vivo structural MRI studies (Estruch et al., 1997; Pfefferbaum et al., 1992, 1995, 1996, 1997; Shear et al., 1994; Sullivan et al., 2000). In line with these findings, postmortem Ribonucleic acid (RNA) analyses in the superior frontal lobe samples observed that genes related to myelin structure were down-regulated in alcoholics (Lewohl et al., 2000). Although this is the first study, which revealed WM volume reduction in the reward system among alcoholic subjects, the alcohol's effect on WM, especially in the reward system is needed to be further clarified.

GM consists of cell bodies in the cortex and subcortical nuclei and WM consists of myelinated axons that connect the neurons of the cerebral cortex to each other. It means the shrinkage of GM is related to brain volume decrease due to neuronal cell death. On the other hand, the reduction of WM is affected by myelin sheath deterioration. We found both neuronal degeneration and axonal degeneration among alcoholic patients. It is known that neuronal degeneration is induced by neurotoxic effect of alcohol (Liput et al., 2017) and axonal degeneration is attributed to thiamine deficiency rather than neurotoxic effect of alcohol (Koike et al., 2003). The patients participated in the study were abstinent alcoholics in treatment and did not show thiamine deficiency. Therefore, it is assumed that WM has been recovered and GM in most ROIs was still decreased among the patients compared to the controls. For this reason, it seems that WM does not show much difference as much as GM does between the alcohol and the control groups.

The study has a few limitations. First, it is hard to demonstrate whether the decreased volumes of these areas are due to the neurotoxic effects of alcohol or, conversely, if these changes signify a risk factor, predisposing individuals to alcoholism. Second, using the 4 mm slice thickness was too large to measure brain volumetry. In the future study, applying the smaller slice thickness can help obtaining more precise data for brain volumetry. Third, the sample size of 16 individuals in each group was small. The small sample size might restrict for us to find the relationship between the alcoholism and the brain volume reduction. We calculated the effect size, which is an objective indicator on how much difference there is between the alcohol and control groups. The proposed indicator is Cohen's *d* as included in the Table 2 and 3 of the result section. All of the calculated Cohen's *d* values were found to have high effect size above medium so that the statistical power was found to be high in the study (Cohen, 1988). Although the sample size is small, the result seems to achieve sufficient statistical power. Fourth, brain volume reduction of the right and left hemispheres are not included in the study

by distinguishing right from left in each ROI. In previous studies, it was assumed that lateralization would be present in addiction (Oscar-Berman & Marinković, 2007), but the results on lateralization in addiction are inconsistent (Benegal et al., 2007; Grodin et al., 2013; Mechtcheriakov et al., 2007). In the study, we focused to examine venerable regions on the toxic effects of alcohol rather than to identify the effect of lateralization in the changes of brain structure among alcoholic patients. However, further studies should include brain volume reduction on right and left hemispheres, and it is necessary to discuss on the results deeply.

Despite the limitations, we found a regional volume reduction both in the GM and in WM of the reward system using VBM. The results suggest patients with alcohol dependency have volumetric deficits in the brain's extended reward and oversight system. Further research is required to investigate a causal relationship between alcohol consumption and regional brain atrophy.

REFERENCES

Agartz, I., Momenan, R., Rawlings, R. R., Kerich, M. J., & Hommer, D. W. (1999). Hippocampal volume in patients with alcohol dependence. *Archives of General Psychiatry*, *56*(4), 356-363. DOI: 10.1001/archpsyc.56.4.356

American Diabetes Association (2009). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, *32*(Suppl. 1), S62-7. https://doi.org/10.2337/dc14-S081

Ashburner, J., & Friston, K. J. (2001). Why Voxel-based morphometry should be used. *Neuroimage*, *14*(6), 1238-1243. DOI: 10.1006/nimg.2001.0961

Benegal, V., Antony, G., Venkatasubramanian, G., & Jayakumar, P. N. (2007). Imaging study: gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. *Addiction Biology*, *12*(1), 122-132. DOI: 10.1111/j.1369-1600.2006.00043.x

Beresford, T. P., Arciniegas, D. B., Alfers, J., Clapp, L., Martin, B., Du, Y., & Davatzikos, C. (2006). Hippocampus volume loss due to chronic heavy drinking. *Alcoholism: Clinical and Experimental Research*, *30*(11), 1866-1870. DOI: 10.1111/j.1530-0277.2006.00223.x

Blum, K., Sheridan, P. J., Wood, R. C., Braverman, E. R., Chen, T. J., Cull, J. G., & Comings, D. E. (1996). The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. *Journal of the Royal Society of Medicine*, *89*(7), 396-400.

Bookstein, F. L. (2001). Voxel-based morphometry should not be used with imperfectly registered images. *Neuroimage*, *14*(6), 1454-1462. DOI: 10.1006/nimg.2001.0770

Bowirrat, A., & Oscar-Berman, M. (2005). Relationship between dopaminergic neurotransmission, alcoholism, and reward deficiency syndrome. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *132*(1), 29-37. DOI: 10.1002/ajmg.b.30080

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Corbit, L. H., & Balleine, B. W. (2005). Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of pavlovian-instrumental transfer. *The Journal of Neuroscience*, *25*(4), 962-970. DOI: 10.1523/JNEUROSCI.4507-04.2005

Davis, K. D., Taylor, K. S., Hutchison, W. D., Dostrovsky, J. O., McAndrews, M. P., Richter, E. O., & Lozano, A. M. (2005). Human anterior cingulate cortex neurons encode cognitive and emotional demands. *The Journal of Neuroscience*, *25*(37), 8402-8406. DOI: 10.1523/JNEUROSCI.2315-05.2005

Ding, J., Eigenbrodt, M. L., Mosley, T. H. Jr, Hutchinson, R. G., Folsom, A. R., Harris, T. B., & Nieto, F. J. (2004). Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-

based population of middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*, *35*(1), 16-21. DOI: 10.1016/S0022-510X(96)00298-5 http://stroke.ahajournals.org/content/35/1/16

Estruch, R., Nicolas, J. M., Salamero, M., Aragon, C., Sacanella, E., Fernandez-Sola, J., & Urbano-Marquez, A. (1997). Atrophy of the corpus callosum in chronic alcoholism. *Journal of the Neurological Sciences*, *146*(2), 145-151. DOI: 10.1016/S0022-510X(96)00298-5

Fuster, J. M. (1997). *The prefrontal cortex, anatomy, physiology, and neuropsychology of the frontal lobe.* Philadelphia: Lippincott-Raven.

Fuster, J. M. (2003). *Cortex and mind*. New York: Oxford University Press.

Fuster, J. M. (2006). The cognit: a network model of cortical representation. *International Journal of Psychophysiology*, *60*(2), 125-132. DOI: 10.1016/j.ijpsycho.2005.12.015

Grodin, E. N., Lin, H., Durkee, C. A., Hommer, D. W., & Momenan, R. (2013). Deficits in cortical, diencephalic and midbrain gray matter in alcoholism measured by VBM: Effects of co-morbid substance abuse. *NeuroImage: Clinical*, *2*, 469-476. DOI: 10.1016/j.nicl.2013.03.013

Grusser, S. M., Wrase, J., Klein S., Hermann, D., Smolka, M. N., Ruf, M., Weber-Fahr, W., Flor, H., Mann, K., Braus, D. F., & Heinz, A. (2004). Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology*, *175*(3), 296-302. DOI: 10.1007/s00213-004-1828-4

Heimer, L., & Van Hoesen, G. W. (2006). The limbic lobe and its output channels: implications for emotional functions and adaptive behavior. *Neuroscience & Biobehavioral Reviews*, *30*(2), 126-147. DOI: 10.1016/j.neubiorev.2005.06.006

Herlidou-Meme, S., Constans, J. M., Carsin, B., Olivie, D., Eliat, P. A., Nadal-Desparats, L., Gondry, C., Le Rumeur, E., Idy-Peretti, I., & de Certaines, J. D. (2003). MRI texture analysis on texture test objects, normal brain and intracranial tumors. *Magnetic Resonance Imaging*, *21*(9), 989-993. DOI: 10.1016/S0730-725X(03)00212-1

Hill, S. Y., De Bellis, M. D., Keshavan, M. S., Lowers, L., Shen, S., Hall, J., & Pitts, T. (2001). Right amygdala volume in adolescent and young adult offspring from families at high risk for developing alcoholism. *Biological Psychiatry*, *49*(11), 894-905. DOI: 10.1016/S0006-3223(01)01088-5

Herrera, D. G., Yague, A.G., Johnsen-Soriano, S. Bosch-Morell, F., Collado-Morente, L., Muriach, M., Romero, F. J., & García-Verdugo, J. M. (2003). Selective impairment of hippocampal neurogenesis by chronic alcoholism: protective effects of an antioxidant. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(13), 7919-24. DOI: 10.1073/pnas.1230907100

Hornak J., Rolls, E. T., & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia*, *34*(4), 247-261. DOI: 10.1016/0028-3932(95)00106-9

Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., Casanova, R., Deibler, A. R., Burdette, J. H., ..., & Laurienti, P. J. (2007). Relating imaging indices of white matter integrity and volume in healthy older adults. *Cerebral Cortex*, *18*(2), 433-442. DOI: 10.1093/cercor/bhm080

Jones, D. K., Symms, M. R., Cercignani, M., & Howard, R. J. (2005). The effect of filter size on VBM analyses of DT-MRI data. *Neuroimage*, *26*(2), 546-554. DOI: 10.1016/j.neuroimage.2005.02.013

Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M. C., Christensen, G. E., Collins, D. L., Gee, J., Hellier, P., Song, J. H., Jenkinson, M., Lepage, C., Rueckert, D., Thompson, P., Vercauteren, T., Woods, R. P., Mann, J. J., & Parsey, R. V. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage*, *46*(3), 786-802. DOI: 10.1016/j.neuroimage.2008.12.037

Koike, H., Iijima, M., Sugiura, M., Mori, K., Hattori, N., Ito, H., ..., & Sobue, G. (2003). Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. *Annals of Neurology*, *54*(1), 19-29. DOI: 10.1002/ana.10550

Koob, G. F. (1999). The role of the striatopallidal and extended amygdala systems in drug addiction. *Annals of the New York Academy of Sciences*, *877*(1), 445-460. DOI: 10.1111/j.1749-6632.1999.tb09282.x

Kornreich, C., Blairy, S., Philippot, P., Hess, U., Noel, X., Streel, E., Le Bon, O., Dan, B., Pelc, I., & Verbanck, P. (2001). Deficits in recognition of emotional facial expression are still present in alcoholics after mid- to long-term abstinence. *Journal of Studies on Alcohol*, *62*(4), 533-542. DOI: 10.15288/jsa.2001.62.533

LaBar, K. S., & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews. Neuroscience*, *7*(1), 54-64. DOI: 10.1038/nrn1825

Laakso, M. P., Vaurio, O., Savolainen, L., Repo, E., Soininen, H., Aronen, H. J., & Tiihonen, J. (2000). A volumetric MRI study of the hippocampus in type1 and 2 alcoholism. *Behavioural Brain Research*, *109*(2), 177-186. DOI: 10.1016/S0166-4328(99)00172-2

Lewohl, J. M., Wang, L., Miles, M. F., Zhang, L., Dodd, P. R., & Harris, R. A. (2000). Gene expression in human alcoholism: microarray analysis of frontal cortex. *Alcoholism: Clinical and Experimental Research*, *24*(12), 1873-1882. DOI: 10.1111/j.1530-0277.2000.tb01993.x

Liput, D. J., Pauly, J. R., Stinchcomb, A. L., & Nixon, K. (2017). Binge Alcohol Exposure Transiently Changes the Endocannabinoid System: A Potential Target to Prevent Alcohol-Induced Neurodegeneration. *Brain Sciences*, *7*(12), 158. DOI: 10.3390/brainsci7120158

Makris, N., Oscar-Berman, M., Jaffin, S. K., Hodge, S. M., Kennedy, D. N., Caviness, V. S., & Harris, G. J. (2008). Decreased volume of the brain reward system in alcoholism. *Biological Psychiatry*, *64*(3), 192-202. DOI: 10.1016/j.biopsych.2008.01.018

Mechtcheriakov, S., Brenneis, C., Egger, K., Koppelstaetter, F., Schocke, M., & Marksteiner, J. (2007). A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*(6), 610-614. DOI: 10.1136/jnnp.2006.095869

Moselhy, H. F., Georgiou, G., & Kahn, A. (2001). Frontal lobe changes in alcoholism: a review of the literature. *Alcohol and Alcoholism, 36*(5), 357-68. DOI: 10.1093/alcalc/36.5.357

Mechelli, A., Price, C. J., Friston, K. J., & Ashburner, J. (2005). Voxel-based morphometry of the human brain: methods and applications. *Current Medical Imaging Reviews*, *1*(2), 105-113. DOI: 10.2174/1573405054038726

Myrick, H., Anton, R. F., Li, X., Henderson, S., Drobes, D., Voronin, K., & George, M. S. (2004). Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. *Neuropsychopharmacology*, *29*(2), 393-402. DOI: 10.1038/sj.npp.1300295

Nixon, S. J., & Parsons, O. A. (1990). Application of the Tridimensional Personality Questionnaire to a population of alcoholics and other substance abusers. *Alcoholism: Clinical and Experimental Research*, *14*(4), 13-517. DOI: 10.1111/j.1530-0277.1990.tb01190.x

Obernier, J. A., Bouldin, T. W., & Crews, F. T. (2002). Binge ethanol exposure in adult rats causes necrotic cell death. *Alcoholism: Clinical and Experimental Research*, *26*(4), 547-57. DOI: 10.1111/j.1530-0277.2002.tb02573.x

Oscar-Berman, M., & Bowirrat, A. (2005). Genetic influences in emotional dysfunction and alcoholism-related brain damage, *Neuropsychiatr Dis Treat*, *1*(3), 211-229.

Oscar-Berman, M., & Marinković, K. (2007). Alcohol: effects on neurobehavioral functions and the brain. *Neuropsychology Review*, *17*(3), 239-257.

Pentney, R. J. (1991). Remodeling of neuronal dendritic networks with aging and alcohol. *Alcoholism:*

Clinical and Experimental Research, 1, 393-397.

Pfefferbaum, A., Adalsteinsson, E., & Sullivan, E. V. (2005). Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. *Neuroimage*, *26*(3), 891-899. DOI: 10.1016/j.neuroimage.2005.02.034

Pfefferbaum, A., Lim, K. O., Zipursky, R. B., Mathalon, D. H., Rosenbloom, M. J., Lane, B., Ha, C. N., & Sullivan, E. V. (1992). Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcoholism: Clinical and Experimental Research, 16*(6), 1078-1089. DOI: 10.1111/j.1530-0277.1992.tb00702.x

Pfefferbaum, A., Lim, K. O., Desmond, J. E., & Sullivan, E. V. (1996). Thinning of the corpus callosum in older alcoholic men: a magnetic resonance imaging study. *Alcoholism: Clinical and Experimental Research, 20*(4), 752-757. DOI: 10.1111/j.1530-0277.1996.tb01682.x

Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H., Shear, P. K., Rosenbloom, M. J., & Lim, K. O. (1995). Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcoholism: Clinical and Experimental Research, 19*(5), 1177-1191. DOI: 10.1111/j.1530-0277.1995.tb01598.x

Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H., & Lim, K. O. (1997). Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism: Clinical and Experimental Research, 21*(3), 521-529. DOI: 10.1111/j.1530-0277.1997.tb03798.x

Putzke, J., De Beun, R., Schreiber, R., De Vry, J., Tolle, T. R., Zieglgansberger, W., & Spanagel, R. (1998). Long-term alcohol self-administration and alcohol withdrawal differentially modulate microtubule-associated protein 2 (MAP2) gene expression in the rat brain. *Brain Research. Molecular Brain Research*, *62*(2), 196-205. DOI: 10.1016/S0169-328X(98)00253-8

Ridgway, G. R., Henley, S. M. D., Rohrer, J. D., Scahill, R. I., Warren, J. D., & Fox, N. C. (2008). Ten simple rules for reporting voxel-based morphometry studies. *NeuroImage*, *40*(4), 1429-1435. DOI: 10.1016/j.neuroimage.2008.01.003

Shear, P. K., Jernigan, T. L., & Butters, N. (1994). Volumetric magnetic resonance imaging quantification of longitudinal brain changes in abstinent alcoholics. *Alcoholism: Clinical and Experimental Research, 18*(1), 172-176. DOI: 10.1111/j.1530-0277.1994.tb00899.x

Schmahmann, J. D., & Pandya, D. N. (2006). *Fiber pathways of the brain*. New York: Oxford University Press. DOI: 10.1111/j.1468-1331.2007.01833.x

Schaefer, A., Braver, T. S., Reynolds, J. R., Burgess, G. C., Yarkoni, T., & Gray, J. R. (2006). Individual differences in amygdala activity predict response speed during working memory. *The Journal of Neuroscience, 26*(40), 10120-10128. DOI: 10.1523/JNEUROSCI.2567-06.2006

Schneider, F., Habel, U., Wagner, M., Franke, P., Salloum, J. B., Shah, N. J., Toni, I., Sulzbach, C., Hönig, K., Maier, W., Gaebel, W., & Zilles, K. (2001). Subcortical correlates of craving in recently abstinent alcoholic patients. *American Journal of Psychiatry, 158*(7), 1075-1083. DOI: 10.1176/appi.ajp.158.7.1075

Sullivan, E. V., Deshmukh, A., Desmond, J. E., Lim, K. O., & Pfefferbaum, A. (2000). Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: relation to ataxia. *Neuropsychology*, *14*(3), 341-352. DOI: 10.1037/0894-4105.14.3.341

Sullivan, E. V., Marsh, L., Mathalon, D. H., Lim, K. O., & Pfefferbaum, A. (1995). Anterior hippocampal volume deficits in nonamnesic, aging chronic alcoholics. *Alcoholism: Clinical and Experimental Research, 19*(1), 110-122. DOI: 10.1111/j.1530-0277.1995.tb01478.x

Sun, A. Y., Simonyi, A., & Sun, G. Y. (2002). The ''French Paradox'' and beyond: neuroprotective effects of polyphenols. *Free Radical Biology & Medicine*, *32*(4), 314-18. DOI: 10.1016/S0891-5849(01)00803-6

Szabo, Z., Owonikoko, T., Peyrot, M., Varga, J., Mathews, W. B., Ravert, H. T., Dannals, R. F., & Wand, G. (2004). Positron emission tomography imaging of the serotonin transporter in subjects with a history of alcoholism. *Biological Psychiatry, 55*(7), 766-771. DOI: 10.1016/j.biopsych.2003.11.023

Swanson, L. W. (2003). The amygdala and its place in the cerebral hemisphere. *Annals of the New York Academy of Sciences, 985*(1), 174-184. DOI: 10.1111/j.1749-6632.2003.tb07081.x

Tarnowska-Dziduszko, E., Bertrand, E., & Szpak, G. M. (1995). Morphological changes in the corpus callosum in chronic alcoholism. *Folia Neuropathol*, *33*(1), 25-29.

Uekermann, J., Daum, I., Schlebusch, P., & Trenckmann, U. (2005). Processing of affective stimuli in alcoholism. *Cortex*, *41*(2), 189-194. DOI: 10.1016/S0010-9452(08)70893-1

Volkow, N. D., Wang, G. J., Overall, J. E., Hitzemann, R., Fowler, J. S., Pappas, N., Frecska, E., & Piscani, K. (1997). Regional brain metabolic response to lorazepam in alcoholics during early and late alcohol detoxification. *Alcoholism: Clinical and Experimental Research, 21*(7), 1278-1284. DOI: 10.1111/j.1530-0277.1997.tb04449.x

Yassa, M. A., & Stark, C. E. (2009). A quantitative evaluation of cross-participant registration techniques for MRI studies of the medial temporal lobe, *Neuroimaging*, *44*(2), 319-327. DOI: 10.1016/j.neuroimage.2008.09.016

원고접수: 2017.11.14
수정접수: 2017.12.07
게재확정: 2017.12.12