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Prefrontal Cortical Thickness Deficit in Detoxified Alcohol-dependent Patients

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Alcohol dependence is a serious disorder that can be related with a number of potential health-related and social consequences. Cortical thickness measurements would provide important information on the cortical structural alterations in patients with alcohol dependence. Twenty-one patients with alcohol dependence and 22 healthy comparison subjects have been recruited and underwent high-resolution brain magnetic resonance (MR) imaging and clinical assessments. T1-weighted MR images were analyzed using the cortical thickness analysis program. Significantly thinner cortical thickness in patients with alcohol dependence than healthy comparison subjects was noted in the left superior frontal cortical region, correcting for multiple comparisons and adjusting with age and hemispheric average cortical thickness. There was a significant association between thickness in the cluster of the left superior frontal cortex and the duration of alcohol use. The prefrontal cortical region may particularly be vulnerable to chronic alcohol exposure. It is also possible that the pre-existing deficit in this region may have rendered individuals more susceptible to alcohol dependence.

Key words: Alcoholism, Cerebral Cortex, Frontal Lobe, Magnetic Resonance Imaging

INTRODUCTION

Alcohol dependence is the most prevalent substance use disorder [1] that can lead individuals with the disorder to serious health-related [2, 3] and social problems [4, 5]. According to a report by Nutt and colleagues (2007), the level of potential harm and risk of alcohol use and misuse was among the top five with heroin and cocaine [6]. The 12-month prevalence of alcohol dependence is

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reported to be approximately 2% to 6% in the general populations [7-9].

In part reflecting the high potential harm and high prevalence of alcohol dependence, there have been a number of studies on how chronic alcohol use or alcohol dependence interacts with the structure of the brain of animals [10-13] and humans [14-21]. Overall brain atrophy, including the lesser volumes of gray matter and white matter with increased cerebrospinal fluid, in patients with alcohol use disorders, has consistently been reported [22-24]. Deficits in the prefrontal cortex [16, 25], temporal cortex [14, 20, 26], cerebellum [14], striatum, hippocampus and amygdala [14, 27-29] have also been reported in patients with alcohol dependence. Neuropathological studies have shown that the alcohol-related neuronal and glial loss would preferentially involve the prefrontal cortex [30, 31] among cortical regions. Functional neuroimaging studies demonstrated altered metabolism or activation of the frontal cortex in association with the deteriorated neuropsychological functioning [32-34].

Cortical thickness analysis, a reliable and valid method [35, 36], can capture important information on cortical structures [37]. However, relatively few studies have investigated cortical thickness in alcohol-dependent adults [38-40]. Durazzo and colleagues exhibited that alcohol-dependent adults had thinner cortical regions in the left anterior cingulate cortex, bilateral frontal cortex, and bilateral insula than healthy controls [38]. Other researchers found that alcohol-dependent adults had reduced cortical thickness in the widespread brain regions of the superior frontal, precentral, postcentral, middle frontal, middle and superior temporal, middle temporal, and the lateral occipital cortex than healthy comparison participants [39]. In the report by Momenan and colleagues, participants with alcohol dependence exhibited thinner cortical regions that encompass the medial superior frontal cortex, insula, precentral and the precuneus of the right hemisphere as well as the superior frontal gyrus of the left hemisphere, in comparison with the healthy controls [40].

Previous studies have reported widespread cortical deficits without covarying out the effects associated with the global atrophy of the brain [38-40]. Among these widespread regions that show alcohol-related atrophy, we wanted to localize the cortical regions that may be particularly vulnerable to alcohol consumption. We therefore undertook the cortical thickness analysis adjusting for the hemispheric average cortical thickness, in 21 detoxified alcohol-dependent patients and matched 22 healthy comparison subjects. The objective of this study was to identify brain regions with cortical thickness alterations that exceed the level of global alterations in alcohol dependence. We used the whole brain-wise cortical thickness analysis, which is validated histologically [36] and with manual outlining method [35]. We also investigated whether the magnitude of deficits are correlated with the alcohol use-related variable.

Given the studies that suggest the preferential involvement of prefrontal cortex among brain structural and functional alterations in alcohol dependence [16, 25, 31-33, 41, 42], we hypothesized that patients with alcohol dependence would have thinner prefrontal cortex in comparison with healthy comparison subjects, after correcting for the global cortical thinning associated with alcohol dependence.

MATERIALS AND METHODS

Subjects

Patients with alcohol dependence were enrolled from the Inpatient Unit of the Department of Neuropsychiatry in a university-affiliated hospital, Seoul, South Korea. Age-matched healthy comparison subjects were recruited from the community via the local advertisement during the same study period. Age was matched at the group-level. This study was performed from January 2007 to January 2009.

Inclusion criteria for alcohol dependence group were (1) age between 20 and 70, and (2) diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders-IV by 2 board-certified psychiatrists.

Exclusion criteria for both alcohol dependence and control groups were (1) any symptoms or signs of confusion, major medical disorders including kidney disease and chronic liver disease, and/or malnutrition, (2) presence or history of neurological disorders, (3) presence or history of any mental disorders other than alcohol dependence or comorbid depressive disorders, including alcohol-induced persistent dementia, alcohol-induced amnestic disorder, or alcohol withdrawal delirium (3) history of head injury, and (4) any contraindications to magnetic resonance imaging (MRI) such as pace makers, claustrophobia, or metal implants.

Additional exclusion criteria for control group were (1) presence or history of mental disorders including alcohol abuse and (2) current alcohol consumption greater than 14 equivalent standard drinks for men, 7 for women, per time [43].

After being detoxified for 2 weeks, all patients underwent physical examination by a physician and the routine laboratory tests to screen out any major medical disorders. Clinical evaluation was performed by a board-certified psychiatrist. MRI evaluations were performed under the supervision of the key investigators. The study was approved by the University Institutional Review Board. All subjects provided written informed consent before

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study participation.

Brain magnetic resonance (MR) image acquisition and cortical thickness analysis

T1 and T2 weighted MR images were obtained using 1.5 Tesla Siemens whole body scanner. T1 weighted images of 43 subjects were obtained with following image acquisition protocol. Repetition time [TR]=2,050 ms, echo time [TE]=4.39 ms, inversion time [TI]=1,100 ms, number of excitation [NEX]=2, flip angle [FA]=15°, slice thickness=1.3 mm, field of view [FOV]=180×180 mm, acquisition matrix=256×180. T1 weighted images of 7 subjects were obtained with slightly different image acquisition protocol (TR=1,960 ms, TE=4.38 ms, TI=1,100 ms, NEX=2, flip angle [FA]=15°, slice thickness=1.5 mm, FOV=250 X 250, acquisition matrix=256 X 180). T2 weighted images were acquired in order to screen for gross brain abnormality (TR=9,710 ms, TE=120 ms, NEX=2, flip angle [FA]=170°, slice thickness=3 mm).

Measurements of cortical thickness were conducted by using the cortical surface-based analysis [44, 45]. Detailed procedures of the cortical thickness analysis are described elsewhere [46]. Smoothing processes were conducted using an iterative nearest-neighbor averaging procedure with the full-width half maximum (FWHM) 15 mm 2-D Gaussian kernel [45].

Statistical analysis

For calculating statistical difference maps of cortical thickness between alcohol dependence and healthy comparison groups, general linear model (GLM) with cortical thickness at each vertex as the dependent variable has been used. Non-cortical areas of medial wall and corpus callosum were excluded from the model building [47, 48]. Hemispheric average cortical thickness was included in the model as a covariate since there was a significant difference in hemispheric average cortical thickness between groups and our aim was to identify the particularly vulnerable cortical regions beyond the global brain atrophy associated with alcohol dependence. Age was also included as a covariate. To correct for multiple comparisons, 5,000 permutation simulations have been performed with random group-label shuffling, with a threshold for a significant vertex of $p<0.05$ [49, 50]. Clusters with the size that would pass the family-wise error rate correction were considered significant [50].

Thickness values of the surface point with highest z values (local maxima) within the cluster, where significant group differences of cortical thickness were found, were extracted for *post hoc* analyses. Pair-wise correlations were used to test whether there were associations between the magnitude of cortical thickness deficits in patients with alcohol dependence and the duration of alcohol use [21].

Considering the relatively modest sample size, sensitivity analyses to rule out the possibility that the current results may be modulated by other confounding factors such as comorbid depression, anxiety symptoms and scan parameter difference were performed [51, 52]. Local maxima thickness values within the cluster extracted as described above were subjected to linear regression models that included the scan parameter difference, the presence of comorbid depression as defined by 19 or more scores on the 17-item Hamilton Depression Rating Scale (HDRS) [53], or the presence of anxiety as defined by 40 or more scores on the State-Trait Anxiety Inventory (STAI-T) [54, 55] as additional covariates.

Data are presented as means±standard deviations. Computations were performed using STATA version 11 (Stata corp., College Station, TX, USA). Two-tailed $p<0.05$ was considered significant.

RESULTS

There were no significant differences in age and sex between diagnostic groups (Table 1). Patients with alcohol dependence drank alcohol more frequently and more heavily than healthy comparison subjects (Table 1).

Patients with alcohol dependence had general cortical thinning (left hemispheric average cortical thickness (mm): 2.44±0.07 [healthy comparison subjects] vs 2.24±0.27 [patients with alcohol dependence], $t=3.35$, $p=0.002$) (right hemispheric average cortical thickness (mm): 2.45±0.07 [healthy comparison subjects] vs 2.25±0.23 [patients with alcohol dependence], $t=3.77$, $p<0.001$). In order to identify regionally specific cortical deficits in patients with alcohol dependence compared to healthy comparison subjects, hemispheric average cortical thickness was added as a covariate in the whole brain vertex-wise analysis. In the GLM model that includes age and average cortical thickness as covariates, significant cortical thickness deficits in patients with alcohol dependence, compared to healthy comparison subjects, were noted in the left superior frontal cortex, after correcting for multiple comparisons with the permutation method (Fig. 1) (cluster size=1489.5 mm^2; number of vertices in the cluster=2,035; Talairach coordinates=x [-15.3], y [61.8], z [5.0]; cluster p value=0.024).

Given that different scanning parameter may influence on the cortical thickness variations [51], analysis was re-run with scan parameter as a covariate. Trend level significance was noted ($p=0.091$). When analysis was repeated covarying for comorbid depression that may be associated with thinner prefronto-temporal cortex [31, 52, 56], the diagnostic group effect remained

Table 1. Characteristics of participants

Variables	Patients with alcohol dependence (N=21)	Healthy comparison subjects (N=22)	Statistical values		
Demographic variables					
Age, years	50.6 (8.2)	50.2 (8.1)	*t*=0.17	*df*=41	p=0.861
Sex, male/female	18/3	19/3			p=0.645[a]
Alcohol use variables					
Duration of alcohol use, years	32.1 (11.5)	30.0 (8.7)	*t*=0.65	*df*=37	p=0.523
Frequency of alcohol use, times per month	19.4 (8.0)	2.0 (2.2)	*t*=9.71	*df*=37	p<0.001
Average alcohol dose, standard drinks[b] per time	6.9 (3.6)	2.0 (1.8)	*t*=5.53	*df*=37	p<0.001
Alcohol Use Disorders Identification Test (AUDIT) scores	22.1 (7.4)	3.8 (3.7)	*t*=10.06	*df*=37	p<0.001
Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scores	6.8 (8.8)	1.0 (1.1)	*t*=3.10	*df*=37	p=0.004
Other clinical variables					
Comorbid depression[c]	4 (24)	0 (0)			p=0.029[a]
Comorbid anxiety[d]	11 (65)	3 (14)			p=0.002[a]

Data are expressed as mean (standard deviations) or numbers (%).
[a]Fisher's exact test.
[b]One standard drink contains 14 gram of alcohol.
[c]Presence of depression was defined as ≥19 on the 17-item Hamilton Rating Scale for Depression.
[d]Presence of anxiety was defined as ≥40 on the State-Trait Anxiety Inventory.

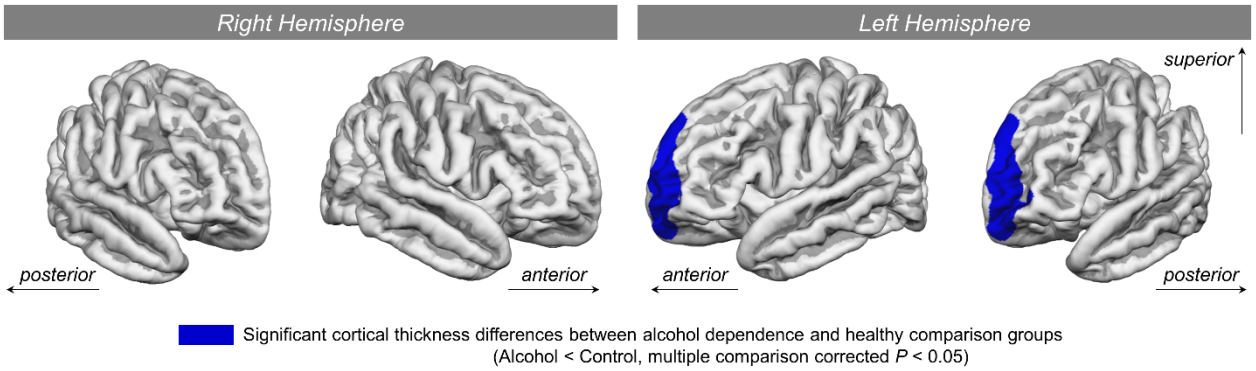

Fig. 1. The cortical region with significant cortical thickness differences between alcohol dependence (N=21) and healthy comparison groups (N=22). Multiple comparisons were corrected using the permutation tests of 5,000 iterations of random shuffling the group labeling. Clusters that pass the threshold for multiple comparison correction with family-wise error correction cluster size inferences are shown here. Covariates were age and hemispheric average cortical thickness.

significant (p=0.001). When analysis was repeated covarying for comorbid anxiety that may also be associated with thinner prefronto-temporal cortex [57, 58], the diagnostic group effect remained significant in the left superior frontal cluster (p=0.017).

Post hoc correlation analysis between cortical thicknesses in the left superior frontal cluster of significant group difference and duration of alcohol use in alcohol dependence group demonstrated the significant association (r=-0.55; p=0.02) (Fig. 2). Cortical thicknesses in the left superior frontal cluster was also correlated with the Clinical Institute Withdrawal Assessment for Alcohol scores (r=-0.548, p=0.028). Otherwise we found no significant results between cortical thicknesses in the left superior frontal cluster and AUDIT scores (r=0.048, p=0.859); and calculated alcohol use (alcohol dose x frequency x duration) (r=-0.193, p=0.509).

DISCUSSION

In the current study, we have identified the brain region with altered cortical thickness in patients with alcohol dependence. The region of cortical thickness deficits in patients with alcohol dependence encompassed primarily the superior frontal cortex, after adjusting for the effects on the global cortical atrophy induced by alcohol dependence (Fig. 1).

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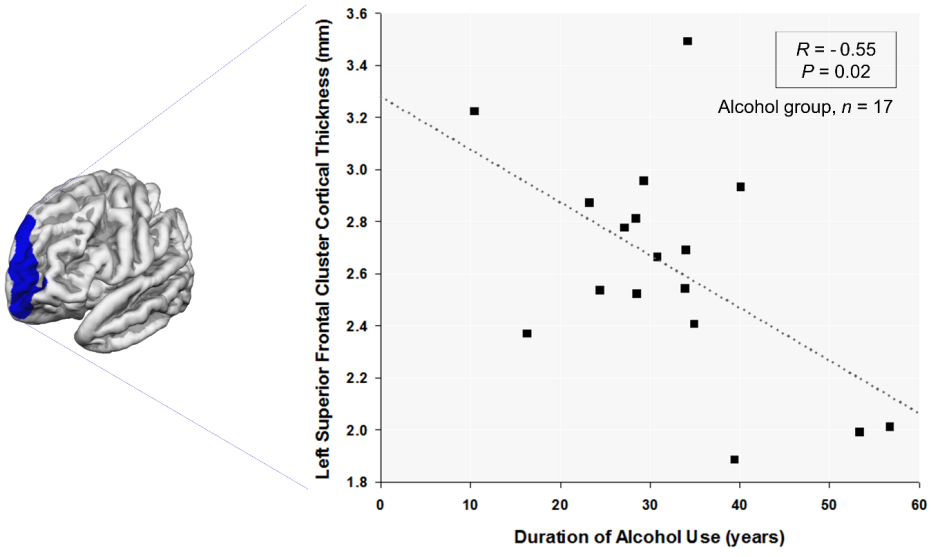

Fig. 2. Correlation between mean cortical thickness of the left superior frontal cortical cluster[a] and duration of alcohol use. [a]This is the cluster where the significant diagnostic group effect was noted after correcting for multiple comparisons using the permutation methods.

This is consistent with prior reports indicating that chronic alcohol use may have the most detrimental effects on prefrontal cortical regions [26, 59, 60]. The level of N-acetyl aspartate, the viability marker of neurons, was decreased in prefrontal brain regions in chronic alcohol abusers [61]. Neuronal and glial loss has consistently been noted in the prefrontal cortical regions, particularly in the superior frontal cortex [30, 62-64]. Alcohol use has been associated with the decreased performances in executive and attention tasks that are important function of the prefrontal cortex [49].

The superior frontal cortex has a key role in the reward circuitry [65]. Pre-existing vulnerability in these regions may predispose individuals to alcohol dependence [65], since the function of these regions are to executively control over drug craving and seeking. These regions may be associated with the compulsive substance-related behaviors [66], which is also in line with our finding that shows the association between duration of alcohol use with the magnitude of the cortical deficits in this region.

The current findings do not provide information regarding whether the pre-existing prefrontal cortical deficits have rendered individuals vulnerable to alcohol dependence [18], whether neurotoxicity of chronic alcohol use, including the oxidative stress [67], have damaged the cortex, or whether both processes have contributed to the observed findings. Supporting evidence for the neurotoxicity as the cause of prefrontal deficits may come from the reports that show patients with longer abstinence have lesser deficits [68]. It has also been suggested that subjects with alcohol dependence may have prefrontal cortex that are less recuperative from toxic effects and may undergo vicious cycle after initial exposure to substances [65, 69]. Considering that alcohol dependence can be divided into two subtypes, type 1 more environmentally influenced, and type 2 more genetically induced [70, 71], a comparison between type 1 and type 2 alcohol dependent patients in a study with larger sample with balanced composition of type 1 and type 2 alcohol dependence may provide an opportunity to approach this question. Longitudinal brain imaging study that follows up patients with alcohol dependence would also provide important insights.

This study alone does not provide direct information as to cellular level mechanisms that may underlie the observed deficits of the cortical thickness. However, there is a vast literature describing the impact of chronic alcohol on the brain [12, 21, 26, 31, 72]. Miguel-Hidalgo and colleagues (2002) reported, in their study with the postmortem brain of alcohol-dependent patients without Wernicke or Korsakoff syndromes, that the glial pathology of reduced size and density was the most characteristic finding. Kril and colleagues (1997) have shown selective loss of non-GABAergic pyramidal neurons. Selective dendritic retraction, rather than cellular death, has been suggested as main pathology related to the volume loss of the gray matter [73].

There is a study that examined the cortical thickness differences in subjects with fetal alcohol syndrome or prenatal alcohol exposure, compared to control subjects [74], which demonstrated deficits in prefronto-temporo-parietal regions. However, few studies have examined cortical thickness in alcohol-dependent adults [38-40]. The cortical thickness analysis has been reported to provide information on an important aspect of the gray matter structure, complementary to the conventional volumetry or the VBM [37, 44, 75]. For example, highly folded regions could have high gray matter density in VBM analysis since there would be

more voxels of gray matter within a fixed radius, but thinner cortical thickness [37]. This is the first study that used cortical thickness analysis in patients with alcohol dependence excluding comorbid substance use, which showed regionally specific cortical thickness deficits in alcohol dependence.

There are limitations of the current study. Relatively modest sample size may limit the generalizability of the findings. Large age range, though covaried in the statistical model, can be another weakness of the study. With the current study of a cross-sectional design, information on whether the observed cortical deficits would be progressive and could be recovered with abstinence cannot be provided. Nicotine dependence, which is highly co-morbid with alcohol dependence, has also been reported to be associated with cortical atrophy, particularly that in frontal cortex [76]. Now that we neither were able to exclude participants with co-morbid nicotine dependence nor delineate the effects of alcohol dependence from those of nicotine dependence, the current results may have been confounded by the effects of chronic nicotine use. Intellectual ability has also been reported to be associated with the prefrontal cortical development [77]. The fact that the intelligence quotient was not included in the statistical model for comparisons of cortical thickness measures, is also an important limitation of the current study. Future studies in larger samples with narrow age range and with neuropsychological assessments for the frontal lobe function, would provide valuable information. Although there could be challenges in following up patients with alcohol dependence, long-term prospective longitudinal study is also warranted.

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