Study on the correlation between prefrontal cortex thickness and alcohol addiction using magnetic resonance imaging in alcohol-dependent patients

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Summary

Objective: To investigate the correlation between alcohol addiction and prefrontal cortex thickness using magnetic resonance imaging (MRI). *Subject and method:* Conducted at the Thai Nguyen National Hospital from 2020 to 2022, the cross-sectional study involved 70 alcohol-dependent individuals and 70 healthy counterparts. Participants, right-handed males, were categorized based on DSM-5 criteria diagnosed with alcoholism or no by a psychiatrist. MRI imaging, employing a Siemens 1.5 Tesla scanner, captured brain structural data. Statistical analysis included Student's t-test and multivariate linear regression models. *Result:* While age and intracranial volume showed no significant differences between healthy and addicted groups, BMI differed significantly. Dorsolateral prefrontal cortex thickness reductions were observed in various regions for the alcoholic group, with significant correlations ($p<0.001$). Age and intracranial volume emerged as predictors for specific regions. *Conclusion:* Alcohol addiction is associated with decreased gray matter thickness in the prefrontal cortex, emphasizing the role of age and intracranial volume in predicting these structural changes. The study underscores the need for further research to comprehensively understand the complexities of alcohol-induced brain damage.

Keywords: Alcohol addiction, prefrontal cortex thickness, multivariable analysis, MRI imaging.

1. Background

Alcohol addiction, as outlined by the National Council on Alcoholism, Drug Dependence, and the American Society of Addiction Medicine (1992), is a chronic and genetically predisposed condition shaped by psychosocial and environmental factors that influence both its development and expression. This condition is marked by a persistent or periodic loss of control during alcohol consumption, a heightened focus on alcohol, continued alcohol use despite negative consequences, and distorted thinking, with denial being particularly prominent [1]. On a global scale in 2016, alcohol addiction stood out as the most widespread among substance use disorders, with an estimated 100.4 million reported cases and 99.2 million adjusted life years lost to disability (constituting 4.2% of the total adjusted life years lost to disability), all attributed to alcohol use [2].

In recent years, there has been a growing emphasis on determining the thickness of the frontal cortex in various psychiatric disorders, particularly in the context of predicting treatment response-a pivotal focus within the field of neuroimaging diagnostics. Addiction, a profound disruption of the brain's reward circuits resulting from heightened stimulation and habitual patterns, manifests as an imbalance in reward function, elevated stress levels, and compromised executive

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function. The inclination towards craving and the compromised executive function observed in alcohol addiction is theorized to be linked with the prefrontal cortex [3].

Hence, the primary objective of this study is to evaluate the correlation between prefrontal cortex thickness and alcohol addiction, utilizing magnetic resonance imaging in individuals affected by alcohol dependency.

2. Subject and method

Data Collection

The cross-sectional study was conducted at the Thai Nguyen National Hospital from 2020 to 2022. Throughout this timeframe, meticulous participant selection focused on right-handed males, and diagnosed alcohol addiction using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5 -2013) [4]. Participants were then categorized into two groups: those with alcohol addiction and those without. Over the 2 years duration, we deliberately paired 70 individuals with alcohol addiction with 70 healthy counterparts, ensuring matching based on predetermined age groups.

Selection criteria

Alcoholism group: Diagnosed with alcoholism by a psychiatrist and being treated at the Department of Psychiatry at the Thai Nguyen National Hospital.

Non-alcoholic group: Purposefully selected (diagnosed as non-alcoholic by a psychiatrist, same age as the alcoholism group) during a health check at the Thai Nguyen National Hospital.

Exclusion criteria included

A history of neurological disorder or other serious physical illness; Those with a history of neurological disorders unrelated to alcohol; a history of drug addiction; a contraindication to MRI…

Images acquisition

We obtained high-resolution brain structural images using a Siemens 1.5 Tesla magnetic resonance imaging (MRI) scanner sourced from Germany. Employing a 3D T1-weighted pulse sequence, specific parameters included 1mm sagittal slices, a repetition time (TR) of 2200ms, an echo time (TE) of 2.93ms, a 30^{o} flip angle, a field of view (FOV) of 256, and an image size of 256 x 256 pixels. Images affected by noise interference or exhibiting detected lesions were meticulously excluded from subsequent analysis.

Processing of MRI data

The DICOM-formatted imaging data underwent conversion to compressed files (file.nii.gz format) using Mango software version 4.0.1. These compressed files were then labeled as Subjxx.nii.gz for further scrutiny through FreeSurfer software (version 6.0, http://surfer.nmr.mgh.harvard.edu) [5], [6]. The 3D images were utilized to compute the thickness of the cerebral cortex throughout the cortical layer. In short, the processing stream included a Talairach transform of each of the subject's native brain, exclusion of non-brain tissue, and separation of grey matter (GM)/white matter (WM) tissue. The GM/WM boundary was tessellated to create multiple vertices across the whole brain. The cortical surface of each hemisphere was enlarged to an average spherical surface to locate the pial surface and the GM/WM boundary. The whole cortex of each subject was visually scrutinized, and topological defects were modified manually, blind to subject identities. Cortical thickness was measured as the shortest distance between the pial surface and the GM/WM boundary at each vertex across the cortical mantle. The mean cortical thickness of each of the 68 regions was calculated using FreeSurfer software [7]. The surface maps were smoothed on the normalized cortical thickness through a Gaussian kernel with a full-width-half-maximum of 10mm.

Research parameters

The study's focal points included age, BMI, intracranial volume (ICV), and the thickness of various brain regions. These encompassed the bilateral superior frontal cortices; the bilateral rostral middle frontal cortices and the bilateral caudal middle frontal cortices.

Data processing

Processing the data involved conducting statistical analysis through the use of Student's t-test, employing analysis packages such as CompareGroups

and MKinfer. In addition, principal component analysis was undertaken to construct a robust multivariate linear regression model, aimed at evaluating the impact of variables such as alcohol dependence, age, BMI, and intracranial volume on dependent variables. The determination of the multivariate model was accomplished using the Stepwise AIC method for optimal model identification. This entire process of optimal model identification was executed using the MASS package in R language version 4.3.0.

Ethical issue

The approval of the Ethics Council of at the Thai Nguyen National Hospital is obtained under number 48/EC-BVTWTN, January 29, 2020.

3. Result

Table 1. Characteristics of the study object

Characteristics	Healthy group (n = 70) (Mean ± SD)	Alcoholic group (n = 70) (Mean ± SD)	p-value*
Age (year)	44.81 ± 8.89	45.51 ± 7.40	0.614
30-39	16 (22.86%)	16 (22.86%)	1.000
40-49	31 (44.29%)	31 (44.29%)	
50-59	19 (27.14%)	19 (27.14%)	
≥ 60	4 (5.71%)	4 (5.71%)	
ICV (mm^3)	1569064.98 ± 136217.11	1558292.91 ± 13070.60	0.612
BMI (kg/m^2)	22.77 ± 2.43	19.91 ± 2.47	<0.001

As per Table 1, there were no statistically significant differences in age and ICV between the groups categorized as healthy and addicted (p>0.05). However, a noteworthy contrast was evident in BMI between the two study groups, with a p-value of < 0.001.

Table 2. Thickness cortical of superior frontal gyrus and middle frontal gyrus according to alcoholism status

Thickness cortical (mm)		Alcohol addiction ($\bar{X} \pm SD$) *		The difference between two groups #		p
		Yes (n = 70)	No (n = 70)	$\bar{X}$	95%CI	
Superior frontal	The left	2.40 ± 0.15	2.59 ± 0.18	-0.19	(-0.24; -0.13)	<0.001
	The right	2.37 ± 0.16	2.59 ± 0.19	-0.22	(-0.28; -0.16)	<0.001
Middle frontal	The left rostral middle frontal	2.11 ± 0.13	2.28 ± 0.14	-0.17	(-0.22; -0.13)	<0.001
	The right rostral middle frontal	2.11 ± 0.13	2.28 ± 0.15	-0.17	(-0.22; -0.13)	<0.001
	The left caudal middle frontal	2.22 ± 0.16	2.34 ± 0.18	-0.12	(-0.18; -0.06)	<0.001
	The right caudal middle frontal	2.24 ± 0.15	2.34 ± 0.16	-0.10	(-0.16; -0.05)	<0.001

*: T-test student; #: the bootstrap *t* test.

Table 2, shows that the alcoholic group had gray matter thickening in the bilateral superior frontal cortices; the bilateral rostral middle frontal cortices and the bilateral caudal middle frontal cortices sides were statistically significantly lower than the control group. Statistically significant differences with p<0.001.

Table 3. Multivariate linear regression model predicting superior frontal thickness

Model			Univariable			Multivariable		
			Estimate	**95% CI**	**p**	**Estimate**	**95% CI**	**p**
The left Superior frontal thickness	Intercept		-	-	-	2.34	(2.30; 2.38)	<0.001
	Alcohol addiction	No	*Reference*			*Reference*		
		Yes	-0.19	(-0.24; -0.13)	<0.001	-0.21	(-0.27; -0.14)	<0.001
	Age (8.16 years)		-0.06	(-0.09; -0.03)	<0.001	-0.06	(-0.09; -0.03)	<0.001
	ICV ($124846mm^3$)		0.02	(-0.01; 0.05)	0.224	0.02	(-0.01; 0.05)	0.150
	BMI (kg/m^2)		0.01	(0.00; 0.02)	0.017	-0.01	(-0.02; 0.00)	0.129
	R^2/R^2 adjusted		-			0.348 / 0.329		
The right superiorfrontal thickness	Intercept		-	-	-	2.80	(2.52-3.08)	<0,001
	Alcohol addiction	No	*Reference*			*Reference*		
		Yes	-0.22	(-0.28; -0.16)	< 0.001	-0.24	(-0.31; -0.18)	<0.001
	Age (8.16 years)		-0.05	(-0.09; -0.02)	< 0.004	-0.05	(-0.08; -0.02)	0.001
	BMI (kg/m^2)		0.02	(0.00-0.03)	0.013	-0.01	(-0.02; 0.00)	0.131
	R^2/R^2 adjusted		-			0.340 / 0.326		

**: Determine the optimal model using Stepwise AIC*

The left superior frontal thickness: As depicted in Table 2, the left superior frontal thickness of the alcoholic group exhibits a reduction of 0.21mm compared to the healthy group, the correlation was statistically significant (p<0.001). Furthermore, the multiple variable linear regression model reveals that as age increased, the left superior frontal thickness decreased, a correlation that remained statistically significant (p<0.001).

The right superior frontal thickness: Analysis presented in Table 2 indicates that the right superior frontal thickness of the Alcoholic group was diminished by 0.24mm relative to the healthy group, the correlation was statistically significant (p<0.001). Additionally, the multiple variable linear regression model reveals that as age increased, the right superior frontal thickness decreased, a correlation that maintained statistical significance (p=0.001).

Table 4. Multivariate linear regression model predicting rostral middle frontal thickness

Model			Univariable			Multivariable		
			Estimate	**95% CI**	**p**	**Estimate**	**95% CI**	**p**
Left rostralmiddle frontal thickness	Intercept		-	-	-	2.28	(2.25; 2.31)	<0.001
	Alcohol addiction	No	*Reference*			*Reference*		
		Yes	-0.17	(-0.22; -0.13)	<0.001	-0.17	(-0.21; -0.13)	<0.001
	Age (8.16 years)		-0.03	(-0.05; -0.00)	0.048	-0.02	(-0.04; -0.00)	0.043
	R^2/R^2 adjusted		-			0.320 / 0.310		
Right rostralmiddle frontal thickness	Intercept		-	-	-	2.28	(2.25; 2.31)	<0.001
	Alcohol addiction	No	*Reference*			*Reference*		
		Yes				-0,17	(-0.22; -0.13)	<0.001
	R^2/R^2 adjusted		-			0.284 / 0.278		

**: Determine the optimal model using Stepwise AIC*

The left rostral middle frontal thickness: According to Table 3, the left rostral middle frontal thickness in the alcoholic group was reduced by 0.17mm compared to the healthy group, the correlation was statistically significant (p<0.001). Furthermore, the multiple variable linear regression model reveals that as age increased, the left rostral middle frontal thickness decreased, a correlation that remains statistically significant (p<0.05).

The right rostral middle frontal thickness: Table 3 demonstrates that the right rostral middle frontal thickness in the alcoholic group was diminished by 0.17mm compared to the healthy group, the correlation was statistically significant (p<0.001).

Table 5. Multivariate Linear Regression Model Predicting caudal middle frontal thickness

Model			Univariable			Multivariable		
			Estimate	**95% CI**	**p**	**Estimate**	**95% CI**	**p**
Left Caudalmiddle frontal thickness	Intercept		-	-	-	2.34	(2.30; 2.38)	<0.001
	Alcohol addiction	No	*Reference*			*Reference*		
		Yes	-0.12	(-0.18; -0.06)	<0.001	-0.11	(-0.17; -0.06)	<0.001
	Age (8.16 years)		-0.04	(-0.07; -0.01)	0.014	-0.04	(-0.06; -0.01)	0.007
	ICV ($124846mm^3$)		0.05	(0.02; 0.08)	0.002	0.05	(0.02; 0.07)	0.001
	R^2/R^2 adjusted		-			0.216 / 0.199		
Right Caudalmiddle frontal thickness	Intercept		-	-	-	2.52	(2.27; 2.76)	<0.001
	Alcohol addiction	No	*Reference*			*Reference*		
		Yes	-0,01	(-0.16; -0.05)	<0.001	-0.12	(-0.18; -0.06)	<0.001
	Age (8.16 years)		-0.02	(-0.05; 0.00)	0.074	-0.03	(-0.05; -0.00)	0.038
	ICV ($124846mm^3$)		0.03	(0.00; 0.06)	0.036	0.03	(0.00; 0.05)	0.030
	BMI (kg/m^2)		0.00	(-0.00; 0.01)	0.311	-0.01	(-0.02; 0,00)	0.146
	R^2/R^2 adjusted		-			0.165 / 0.140		

**: Determine the optimal model using Stepwise AIC*

The left caudal middle frontal thickness: In Table 4, it was evident that the left caudal middle frontal thickness in the alcoholic group was 0.11mm lower than that in the healthy group, the correlation was highly statistically significant ($p<0.001$). The multiple variable linear regression model reveals that as age increased, the left caudal middle frontal thickness decreased. Furthermore, an increase in intracranial volume was associated with an increase in left caudal medial frontal thickness, and this correlation maintained statistical significance.

The right caudal middle frontal thickness: Examination of Table 4 reveals that the right caudal middle frontal thickness in the alcoholic group was 0.12mm lower than that in the healthy group, the correlation is highly statistically significant ($p<0.001$). The model also suggests that as age increased, the right caudal middle frontal thickness decreased. Additionally, an increase in intracranial volume was associated with an increase in right caudal medial frontal thickness, and this correlation maintained statistical significance.

4. Discussion

Scientific studies on alcohol-induced brain damage have reported deficits in executive functions, with the prefrontal cortex, particularly the frontal lobe, being the main region responsible for these functions. The superior frontal gyrus and middle frontal gyrus belongs to the dorsolateral frontal cortex. Strengthening behavioral reactions (emotions, memory, judgment, decision-making, etc.) in the reward network is associated with a complex neural network such as the prefrontal cortex. The initial hypothesis was a reduction in the thickness of the dorsolateral frontal cortex in individuals with alcohol addiction.

Current research results indicate that alcohol addiction reduces the gray matter thickness of the bilateral superior frontal cortices; the bilateral rostral middle frontal cortices and the bilateral caudal middle frontal cortices, with significant correlations, $p<0.001$. The results suggest a negative relationship between alcohol addiction and the thickness of the prefrontal cortex.

Age also negatively correlates with gray matter thickness in the prefrontal cortex, including the bilateral superior frontal gyrus, the bilateral the left rostral middle frontal thickness and the left caudal middle frontal thickness, with significant correlations, $p<0.001$. Intracranial volume is a predictor ($p<0.05$) for the bilateral caudal middle frontal thickness.

Durazzo et al. (2011) found significant differences between alcohol-dependent and control groups in the reward system using MANCOVA [$F (16.99) = 3.04$, $p<0.001$]. Age is a predictor ($p<0.01$) for all prefrontal cortex regions; intracranial volume is also a predictor ($p<0.05$) for the right frontal gyrus and left and right lateral orbital gyrus [8]. Stevens et al. (2022) synthesized the results of 19 studies involving 736 individuals with Alcohol Use Disorder (AUD) and 827 control subjects, finding gray matter reduction in areas including the frontal region, parietal region, thalamus, and cerebellum. Particularly, in the late stages of addiction, there was a correlation with the frontal cortex. This supports the association between the frontal cortex and alcohol addiction [9]. Morris et al. (2019) reported a negative relationship between the frequency of heavy alcohol consumption and the thickness of the prefrontal cortex in various prefrontal regions (superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, and frontal pole) using linear regression models (controlling for age, gender, education level, income, smoking, drug use, twin status, and intracranial volume) [10]. However, some studies have not detected structural changes in this region, as seen in the study by Yang et al. (2020), which showed a significant decrease in the thickness of the cortex in the occipital cortex and parietal cortex but did not find changes in the prefrontal cortex. The authors suggested that this may be due to the study's focus on cortical thickness without considering the volume of brain regions, as in previous studies [11]. The research results lack consistency, and this clear difference ensures the need for further in-depth studies.

Alcohol and its acetaldehyde metabolism act as neurotoxic substances, and alcohol addiction causes brain damage through various mechanisms. Nakamura et al. (2003) reported a case post-mortem

where the addictive substance acetaldehyde was found in the frontal cortex and midbrain of an alcohol addict [12]. Nerve cell loss or atrophy of nerve cells and reduced branching of dendrites are believed to lead to the observed decrease in volume and thickness of the observed prefrontal cortex in alcohol dependence [13], [14], [15]. Findings on nerve cell damage in alcohol addicts align with structural images of the nervous system and the frontal lobe, suggesting that these regions may be more susceptible to alcohol-related damage than other cortical areas.

5. Conclusion

Our results provide further compelling evidence for cortical thickness abnormalities in alcohol abuse and propose that symptom severity is a critical factor linked with brain morphological alterations. Alcohol addiction is linked to a reduction in gray matter thickness in various frontal lobe regions. Age also demonstrates a negative correlation with gray matter thickness in these regions, while intracranial volume positive correlation with gray matter thickness infrontal lobe regions.

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