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Extensive Gray Matter Volume Reduction and Correlations with Neuropsychological Performance in Alcohol Use Disorder Patients

Serdar Nurmedov[1], Onur Noyan[2], Baris Metin[2], Sehadet Ekmen[3], Cumhur Avcil[3], Samet Kose[4]

ABSTRACT:

Extensive gray matter volume reduction and correlations with neuropsychological performance in alcohol use disorder patients

Objective: Long term alcohol use results in varying degrees of deficits in cognitive functions. Although the neocortex, particularly the frontal lobe; limbic system and cerebellum are the brain regions most vulnerable to the toxic effects of alcohol, neural correlates of neuropsychological deficits have not been studied directly.
Methods: This voxel based morphometric (VBM) study examined the effect of duration and amount of alcohol exposure on gray matter (GM) volume and the relation between GM volumes and neuropsychological deficits in patients with Alcohol Use Disorder (AUD).
Results: Voxel-wise whole brain analysis showed extensive regional gray matter volume for AUD patients and GM volumes were inversely correlated to the amount of alcohol exposure. More importantly, there were statistically significant correlations between different indices of executive functioning and GM volumes.
Conclusion: These results indicate that dose-dependent alcohol effect on prefrontostriatal and temporal circuitries appears to be directly related to neurocognitive deficits seen in these patients.

Keywords: alcoholism, neurocognitive deficit, gray matter volume, voxel based morphometry

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[1]M.D., Acibadem Healthcare Group, Istanbul - Turkey
[2]M.D., [3]M.Sc.,Uskudar University, Department of Psychology, Istanbul - Turkey
[4]M.D., Ph.D., Department of Psychiatry and Behavioral Sciences Center for Neurobehavioral Research on Addictions, University of Texas Medical School, Houston, Texas, US

Corresponding address:
Dr. Serdar Nurmedov,
Acıbadem Sağlık Grubu, Fahrettin Kerim Gökay Caddesi No: 49, Altunizade, Istanbul - Türkiye

Phone: +90-553-392-7649

E-mail address:
serdarnurmedov@gmail.com

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INTRODUCTION

As mentioned in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), alcohol use disorder (AUD) is defined by a cluster of behavioral and physical symptoms, which can include withdrawal, tolerance, and craving. AUD causes a significant health burden and leads to both direct and indirect mortality and morbidity that can be prevented[1]. At the same time long term alcohol use results in varying degrees of deficits in several cognitive functions. As reported by several studies, the most common alterations are those related to problems of memory, learning, abstraction, problem solving, visio spatial analysis and synthesis, psychomotor speed processing, speed of information processing, and cognitive efficiency. Although these findings indicate that the neocortex, particularly the frontal lobe; limbic system and

cerebellum are the brain regions most vulnerable to the toxic effects of alcohol, no study to date has aimed to identify directly which brain regions are responsible for the neuropsychological performance deficits seen in AUD[2-5].

Over the past three decades, neuroimaging studies have provided data on the effects of alcohol dependence on the brain's gray matter (GM) volume[6]. Many of these studies utilized the voxel based morphometry (VBM) technique to quantitatively explore the effects of alcohol on GM volumes; these studies have found that the frontal lobes, limbic system and cerebellum are notably vulnerable to damage and dysfunction. These brain regions are associated with reward, motivation, memory, and fine motor control[7-9]. However there is considerable variation in terms of reported GM changes from one study to another. Therefore, Xiao et al.[10] conducted a meta-analysis of nine VBM studies aiming to examine the concurrence across various VBM studies to help clarify the structural abnormalities underlying this condition. Xiao et al.[10] identified that regional GM atrophy involving the prefrontal cortex including the anterior cingulate cortex (ACC), dorsal striatum/ insula, and the posterior cingulate and these were consistent across all the studies[8-13].

Despite ample evidence for GM reduction in AUD, only a few studies examined the correlation between drinking history, amount of alcohol consumption, and structural alterations in the brain. Ruiz et al.[14] showed that years of heavy drinking had a strong negative impact on the corpus callosum, while abstinence duration was associated with larger corpus callosum volumes in alcoholic men.

McQueeny et al.[15] identified that binge drinkers had lower fractional anisotropy than controls in 18 white matter areas and lower fractional anisotropy in six of these regions was linked to significantly greater lifetime hangover symptoms of higher estimated peak blood alcohol concentrations. Chanraud et al.[16] using VBM, reported that the age of first drinking was linked to decreased gray matter volume in the frontal cortex, cerebellum, and pons. The correlation between the extent of alcohol exposure and GM volumes is of importance due to the fact that significant correlation would indicate that GM reduction in a specific region is a direct result of alcohol exposure and the absence of a significant correlation would suggest that the GM alterations are more likely to be related to alcohol use disorder susceptibility in these individuals.

In this study, we hypothesized that there are volume alterations in some brain regions especially in frontal lobe in AUD patients with neuropsychological deficits and we aimed to identify the neural correlates of the amount of alcohol exposure with neuropsychological deficits in AUD. First, we identified GM reductions in AUD patients by comparing their brain images to healthy controls using the VBM method. Then, we explored the relationship between the GM volumes in brain regions showing statistically significant group differences and indices of alcohol exposure and neuropsychological performance.

METHODS

Study Sample

We examined the medical records of patients that were treated in an addiction clinic in Istanbul, Turkey between January 2014 and April 2015. The medical records of 52 patients were examined and 28 were excluded due to lack of sufficient data. Participants who had another psychiatric disorder, a past or current substance use disorder other than nicotine, neurological disease, dementia, Wernicke Encephalopathy, Korsakoff 's syndrome, and a history of head trauma were excluded. The use of alcohol and other illegal drugs in the previous 3-4 days was excluded by an immunoassay urine test. All participants were diagnosed as having alcohol use disorder, based on DSM-5 criteria, by two independent psychiatrists. The data derived from patient records included socio-demographic data such as age, gender, marital status, duration of education, age-at-first-alcohol use, total duration of drinking (years), duration of heavy drinking

(years), and daily frequency of alcohol use in the last year. The AUD group consisted of twenty four patients (20 of which were men). The MRI scans were acquired on the day 7 after the last alcohol usage. The comparison group consisted of age and sex matched 23 healthy men and 6 healthy women who had no history of psychopathology and use of any psychoactive drugs. This present study was approved by the Ethical Committee of Uskudar University. Written informed consents were obtained from the participants following the study protocol was thoroughly explained. All participants in the study had done complete biochemical examinations and urine toxicology tests. The control group was comprised of twenty-nine healthy males and females who fulfilled inclusion criteria and they were matched with the AUD study group in terms of age, level of education, and socio-demographic status.

Neuropsychological Assessment

For an assessment of neuropsychological performance, we have chosen three major domains: executive functions, language, and memory. The Stroop test (a test of colors and words) was used for executive functions, the Boston Naming Test (BNT) was used for language and naming, and the Verbal Memory Processes Test (VMPT) was used for verbal learning and memory. Twenty-two patients had data for VMPT and Stroop test and 21 patients had data for BNT. The Stroop test included 3 trials: (1) read words of colors printed in black; (2) name the color of colored patches; (3) name the color of the ink of words designating colors (where the meaning of the words and color of ink were incongruent). This test was based upon the fact that it takes longer to find the name of the color of an ink than to read the word written with this ink. Any errors made and time to read/ name the list of words/ colors was recorded[17].

BNT is most often used as a measure of task of visual confrontation naming, sensitive to deficits in semantic retrieval. The study participant was shown 31 black and white ink pictures from the most to least common and is asked to name them. When the participant is not able to name a drawing, an examiner gives him/ her semantic then phonetic cues[18].

VMPT has proven useful in evaluating verbal learning and memory; including immediate retrieval, process of learning or acquiring knowledge, encoding versus retrieval, and retention of information and recalling. Recalling is evaluated under two categories as delayed spontaneous recalling and delayed recognition memory. The test consists of a list of fifteen unrelated words. The words on the list were read to the participant with an interval of one second between them. The participant was then asked to recall the words. This stage of the test offers information regarding immediate retrieval and sustained attention. The number of words recalled correctly provides the Immediate Memory Score. The sum of words that the participant recalled correctly after each time we read 10 times provides the Total Learning Score. After the first attempt, the same list is read to the participant nine more times, repeating the recalling process after each time. This stage provides information regarding the learning skills of the participant. The validity and reliability study of the Turkish version of VMPT was performed[19].

Structural Magnetic Resonance Image Acquisition

The imaging was performed on a 1.5T MR scanner (Achieva, Philips Healthcare, Best, The Netherlands) with a SENSE-Head-8 coil at NPISTANBUL Neuropsychiatry Hospital, Istanbul. T1- weighted MPRAGE sequence was employed as high-resolution anatomical scan (repetition time=8.6, echo time=4, flip angle=8, voxel size 0.9375 x 0.9375 x 1.2 mm; slice spacing=1.2 mm, field of view=240 x 240mm, matrix = 256 x 256, and 125 slices). Three-dimensional gradient distortion correction was applied to images to correct for non-linear changes in the magnetic field that could lead to image warping. All subjects had good GM/ WM contrast and no or minimal artefact.

VBM Analyses

We examined the between-group differences in gray matter volume by using VBM. The data were processed and examined using the SPM software (Welcome Department of Imaging Neuroscience Group, London, UK (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default preprocessing parameters. Adaptive Nonlocal Means (SANLM)[20] and a classical Markov Random Field (MRF) model[21] were used to remove inhomogeneities and to improve the signal-to-noise ratio. A linear affine transformation and a nonlinear deformation using high-dimensional DARTEL normalization were used for registration to standard MNI-space[22]. Subsequently, normalized GM images were multiplied by the nonlinear components derived from the normalization matrix to preserve actual GM values locally (modulated GM volumes). Unsegmented images were visually inspected to check the quality of the normalization procedure. Sample homogeneities were inspected using covariance to identify outliers (no participant was excluded for being an outlier). Finally, segmented and modulated images were smoothed with an 8-mm fullwidth, half-maximum Gaussian kernel (Figure 1).

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables in the study were compared by chi-square analysis. Descriptive statistics were calculated as frequency and percent. For all analyses, $p<0.05$ was considered significant.

The two groups were compared using the independent sample t-test, as implemented in the SPM second-level model; in addition, age and sex were entered as covariates to the model in VBM analyses. The clusters were deemed significant if they survived FWE correction at a p level of 0.05 (cluster forming threshold= 20 voxels). Finally, in order to identify the associations between structural abnormalities and other variables, we conducted a region of interest (ROI) analysis. ROIs were defined as GM clusters where group differences were identified. GM volumes of ROIs were extracted using the Marsbar toolbox and transfered to the

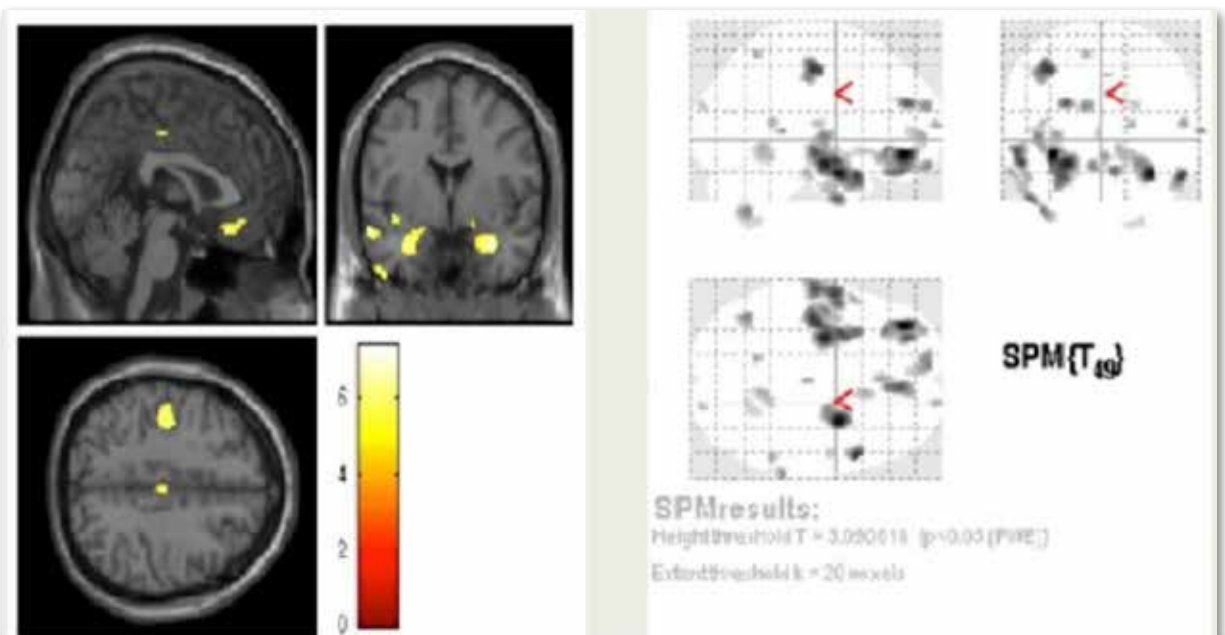

Figure 1: The regions that showed significant GM volume reduction for alcohol group in voxel-wise whole brain analysis. The single subject MR template provided by SPM8 was used as background. The GM volumes in these regions were extracted to perform further statistical analyses.

Table 1: Socio-demographic and clinical characteristics of the participants

	Control group (n=29)	AUD group (n=24)	p
Age (mean±SD)	37.45±10.871	40.79±9.807	
Gender (n, %)			
Male	23 (79.3)	20 (83.3)	0.250
Female	6 (20.7)	4 (16.7)	0.652
Age onset of alcohol use (mean±SD)	-	21.3 (7.98)	
Total duration of drinking (mean±SD)	-	19.0 (9.19)	
Duration of heavy drinking (years. mean±SD)	-	7.7 (4.75)	
Number of alcohol use days in past year (mean±SD)	-	288.8 (64.85)	

Table 2: Gray matter differences between AUD group and control group

	Peak MNI coordinates			T value	Cluster size	p
Frontal lobe						
1. Left inferior frontal gyrus/orbitofrontal cortex	-34.5	45	-12	7.34	781	<0.001
Left inferior frontal gyrus/orbitofrontal cortex	-31.5	31.5	-9	6.18		0.002
Left middle frontal gyrus	-31.5	55.5	1.5	5.69		0.008
2. Left superior frontal gyrus	-12	60	21	5.89	118	0.005
3. Left superior orbital gyrus	-7.5	61.5	-19.5	6.05	111	0.003
4. Left middle frontal gyrus	-25.5	46.5	24	6.41	166	0.001
5. Right rectal gyrus	7.5	42	-22.5	6.38	308	0.001
6. Right superior frontal gyrus	18	67.5	9	5.56	28	0.012
7. Anterior cingulate cortex	-3	49.5	3	5.34	25	0.024
8. Middle cingulate cortex	3	-21	43.5	5.67	26	0.009
9. Ventromedial prefrontal cortex	1.5	28.5	-13.5	5.68	99	0.009
Limbic Areas						
10. Left Hippocampus	-25.5	-10.5	-18	6.98	1807	<0.001
Left Amygdala	-28.5	1.5	-27	6.47		0.001
Left Hippocampus	-33	-10.5	-22.5	6.34		0.001
11. Right amygdala	31.5	0	-25.5	7.19	755	<0.001
Right hippokampus	27	-7.5	-19.5	5.94		0.004
Right amygdala	18	-3	-10.5	5.46		0.017
Temporal lobe						
12. Left middle temporal gyrus	-57	-3	-16.5	6.63	536	<0.001
Left middle temporal gyrus	-58.5	-16.5	-10.5	6.44		0.001
13. Left inferior temporal gyrus	-51	-1.5	-42	6.28	244	0.001
Left inferior temporal gyrus	-58.5	-9	-34.5	5.46		0.017
14. Left middle temporal gyrus	-54	10.5	-27	5.63	42	0.010
15. Left inferior temporal gyrus	-64.5	-22.5	-24	5.57	64	0.012
16. Right temporal pole	54	12	-27	6.76	181	<0.001
17. Right middle temporal gyrus	67.5	-39	4.5	5.91	32	0.004
18. Right middle temporal gyrus	55.5	-46.5	10.5	5.68	40	0.009
19. Right inferior temporal gyrus	52.5	-6	-34.5	5.36	26	0.023
Parietal Lobe						
20. Left postcentral gyrus	-39	-18	48	6.71	462	<0.001
21. Left precuneus	-12	-57	57	5.64	26	0.010
Occipital Lobe						
22. Right superior occipital gyrus	21	-94.5	21	5.43	25	0.019
Cerebellum						
23. Left cerebellum	-40.5	-64.5	-52.5	5.60	135	0.003
24. Right cerebellum	12	-52.5	-9	5.60	191	0.011
Right cerebellum	18	-48	-13.5	5.42		0.019
Right lingual gyrus	10.5	-63	-9	5.11		0.047
25. Right cerebellum	25.5	-60	-58.5	5.24	87	0.032
Right cerebellum	18	-63	-60	5.19		0.038
Basal ganglia						
26. Right ventral striatum	12	18	-10.5	5.57	69	0.012

SPSS statistical software (SPSS Inc., Chicago, IL, USA) for further analysis. Pearson's correlation coefficients were computed between the indices of alcohol exposure, neuropsychological test results and GM volumes in ROIs.

RESULTS

The socio-demographic and the clinical characteristics of participants of the two study groups were presented in Table 1. Comparing the control group with AUD patients, voxel-wise whole brain analysis showed that extensive regional gray matter volume was statistically significantly decreased for AUD patients notably in temporal lobes and hippocampi, prefrontal cortex, parietal areas as well as subcortical structures such as anterior striatum (Table 2, Figure 2).

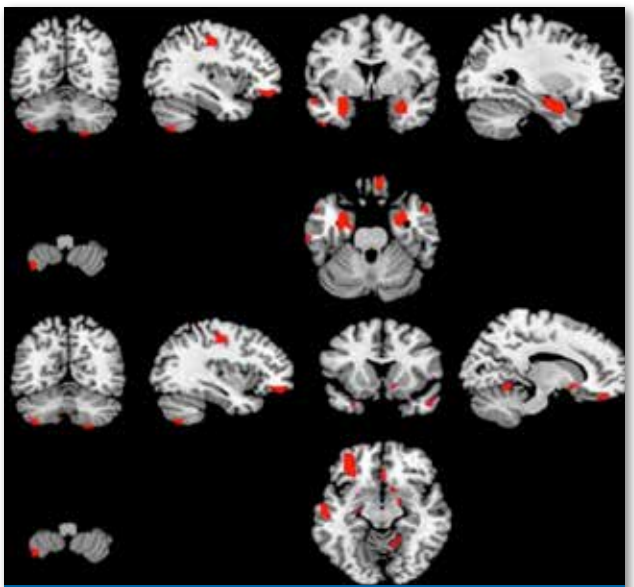

Figure 2: Reduced gray matter volume densities in AUD group compared to healthy control group

In addition various statistically significant correlations were found between different indices of executive functioning, drinking history and gray matter volume reduction. Particularly, duration of heavy drinking was inversely correlated with GM volumes in anterior striatum, parietal lobe, temporal lobe and ventromedial prefrontal cortex (VMPFC). Total duration of drinking was inversely mild-to-moderate correlated with GM volumes in anterior cingulate cortex (ACC), middle cingulate cortex (MCC), hippocampus/ amygdala, anterior striatum, superior frontal gyrus, temporal lobe and VMPFC. The correlation analysis using the number of alcohol-use days in past year (NAUDPY), a variable not confounded by patient age, was also inversely moderate correlated with GM volumes in the ACC, MCC, orbitofrontal, cerebellar, left middle frontal, temporal, VMPFC, hippocampus/ amygdala, and anterior striatum ROI GM volumes. There were no correlations between age of onset of alcohol use with gray matter tissue volumes.

Regarding executive functions; Stroop interference was inversely mild to moderate

Table 3: Correlations between different indices of executive functioning, drinking history, and regional gray matter volume

	Age onset of alcohol use	Duration of heavy drinking	Total duration of drinking	NAUDPY[1]	Stroop interference	BNT Correct[2]	VMPT total[3]
Anterior Cingulate Cortex	0.159	-0.380	-0.536*	-0.482*	-0.334	0.108	0.627*
Hippocampus/Amygdala	0.036	-0.387	-0.421*	-0.411*	-0.433*	-0.042	0.375
Middle Cingulate Cortex	-0.125	-0.183	-0.431*	-0.498*	-0.460*	0.038	0.527*
Occipital	0.132	-0.233	-0.362	-0.233	-0.395	0.021	0.421
Orbitofrontal	-0.042	-0.186	-0.361	-0.472*	-0.398	0.126	0.523*
Parietal	-0.256	-0.412*	-0.379	-0.313	-0.374	0.230	0.535*
Precuneus	-0.128	-0.031	-0.047	-0.167	-0.177	-0.109	-0.025
Anterior striatum	-0.015	-0.435*	-0.473*	-0.407*	-0.351	0.130	0.500*
Cerebellum	-0.153	-0.280	-0.249	-0.416*	-0.456*	0.179	0.196
Left Middle Frontal	0.064	-0.394	-0.383	-0.620*	-0.551*	0.045	0.443*
Superior Frontal	0.020	-0.327	-0.498*	-0.257	-0.455*	0.122	-0.015
Temporal	-0.023	-0.440*	-0.545*	-0.490*	-0.569*	0.396	0.553*
Ventromedial Prefrontal Cortex	0.169	-0.498*	-0.561*	-0.539*	-0.445*	0.333	0.515*

*Correlation is significant at the 0.05 level. 1Number of alcohol-use days in past year. 2Boston Naming Test Total Correct. 3Verbal Memory Processes Test Total Learning Score

correlated with GM volumes in MCC, hippocampus/ amygdala, cerebellum, left middle frontal gyrus, superior frontal gyrus, temporal areas, and VMPFC. Additionally VMPT Total Learning Scores positively mild to moderate correlated with GM volumes in ACC, MCC, orbitofrontal, parietal, temporal, left middle frontal, VMPFC, and anterior striatum. BNT scores were not correlated with the GM volumes (Table 3).

DISCUSSION

In this study, we examined the relationship between changes in GM volume, drinking history and neuropsychological performance in detoxified AUD patients. GM reductions related to AUD were found primarily in prefrontal cortex, limbic system, temporal lobe, anterior striatum, and cerebellum for AUD patients. These areas were consistent with previous VBM studies in AUD patients[10-12].

Additionally we found that the duration of heavy drinking, total drinking duration, and number of alcohol use days in the previous year were inversely related to GM volumes in a number of areas including prefrontal, temporolimbic areas, anterior striatum, and cerebellum. Interestingly the number of alcohol use days in the previous year was correlated to GM volumes in most of the ROIs. Since this variable is independent of age, the significant correlation suggests that age related GM decrease was not a confounding factor. However, there were no correlations between age of onset of alcohol use and GM volume reduction. This last finding is not consistent with a previous study conducted by Chanraud[16], which showed that first drinking at an earlier age was associated with decreased gray matter volumes in the cerebellum, brainstem, and frontal regions. From the regions that are significantly reduced in AUD; the anterior striatum, VMPFC, orbitofrontal cortex belong to the classical reward network. The anterior striatum is the primary area in reward detection as the mesolimbic dopamine fibers originating from ventral tegmental area project to this area and firing of these fibers signal receipt of a reward[23]. This region is also crucially important during the development of addiction as it is involved in processing of drug-related reward signals[24]. Additionally the VMPFC and orbitofrontal cortex are also involved in coding of reward values, comparison of different reward options, and reward expectancy[25,26]. Based on these findings one might suggest that alcohol related reduction in the anterior striatum and other areas in reward circuitry may play in development of alcohol dependence.

Although, there is insufficient research data about verbal learning performance of patients with AUD, in a study about brain response during verbal learning among adolescent users of alcohol and marijuana, it has been found that binge drinkers demonstrated a less BOLD (blood-oxygen-level dependent) response than non-drinkers in the left fusiform gyrus, left precentral gyrus, right middle and inferior frontal gyri, left medial frontal gyrus and cingulate, the left inferior parietal lobule, and precuneus[27]. In this study, we found that the verbal learning performance measured by VMPT was significantly correlated with the reduction in the volume of gray matter in the orbitofrontal, parietal, VMPF, temporal cortices, MCC, the anterior striatum, and the anterior cingulate. VMPT Total Learning Scores were also positively correlated with hippocampus/ amygdala volumes although correlation did not reach statistical significance. These findings may suggest that a verbal learning deficit in AUD is primarily due to frontostriatal dysfunction.

The Stroop Color-Word Task used to examine response inhibition and conflict. Various studies have indicated that the task activates the anterior cingulate cortex, which is known as the primary conflict control area[28-32]. In this study significant correlations were found between stroop interference scores and prefrontal areas including MCC, VMPFC, middle/ superior frontal areas, temporolimbic areas as well as the cerebellum. From these areas, the prefrontal cortex is mainly related to cognitive control while the cerebellum is involved in motor control. Recent studies indicated that temporal lobe was also activated during the stroop task and its role could be semantic processing of task stimuli.

Our study had some limitations. First, the sample size was moderate which might have affected the statistical power of the study. Second, among the executive functions only response inhibition was tested. The correlates of other executive functions such as planning, set shifting would also be interesting to examine and should be explored by future studies. Finally, the number of female participants was insufficient to draw a reliable comparison in terms of gender differences.

In summary, consistent with previous studies we observed widespread GM alterations in AUD including the prefrontal temporal, and parieto-occipital areas. Notably these alterations were correlated to the amount of alcohol exposure and thus they appear to be a direct result of direct alcohol toxicity. Dose-dependent alcohol effect on the prefrontostriatal and temporal circuitries appears to be related to neurocognitive deficits seen in AUD.

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