

Respective influence of current alcohol consumption and duration of heavy drinking on brain morphological alterations in alcohol use disorder

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Abstract

Numerous studies have explored the morphological differences of the brain between subjects with alcohol use disorder (AUD) and control subjects, but very few have investigated the impact of the duration of alcohol use disorder (DAD) and current level of alcohol consumption (CAC) within AUD subjects using magnetic resonance imaging (MRI). We compared the morphological MRI of 44 controls and 66 AUD subjects, recruited at the end of a detoxification program. Additional analyses within the AUD group determined which specific alterations were respectively associated with DAD and CAC using: (1) Bonferroni-corrected multivariable linear regressions to explore the DAD/CAC impact on brain volumes and (2) a general linear model (GLM module of FreeSurfer's Qdec) and Monte Carlo simulation to correct for multiple comparisons ($P < 0.05$) to explore the DAD/CAC impact on cortical thickness and volumes. Analyses were adjusted for age and tobacco use. CAC and DAD were significantly correlated ($\rho = 0.25$, $P < 0.0001$), and sensitivity analyses were conducted with and without both CAC and DAD included in the same model. While the AUD-control comparisons globally reproduced preexisting findings, within-AUD analyses found that CAC was inversely correlated with cortical thickness and gray matter volume in a bilateral dorsal band of the temporal lobe, including the fusiform and parahippocampal gyri. For DAD, only a left and more ventral temporal band that partially overlapped the CAC-associated area was found in cortical thickness analyses. No significant volumetric result was reached after a Bonferroni correction. CAC and, to a lesser extent, DAD were thus associated with specific, though partially overlapping, temporal surface-based signatures.

KEYWORDS

alcoholism, human, neuroimaging

1 | INTRODUCTION

Subjects with alcohol use disorder (AUD) exhibit a wide range of psychological, cognitive, and social impairments, which have underlying structural and functional brain alterations. Compared with healthy

controls, subjects with AUD display volumetric and cortical thickness alterations, including an overall ventricular enlargement and a gray matter reduction of reward-related structures, such as the dorsolateral prefrontal cortex, anterior insula, nucleus accumbens, and the amygdala.¹ However, most studies have focused on the basic comparison

between healthy and AUD individuals, without exploring the heterogeneity of the brain impairments related to AUD. In particular, very little is known regarding variations in structural alterations according to the recent level of alcohol use or the cumulated effect of alcohol on brain over time.

When considered from a dynamic perspective, alcohol-related structural abnormalities might reflect different types of processes. Some alterations could be the expression of vulnerability markers for AUD, being independent of alcohol neurotoxicity and thus quite stable, whereas other alterations might reflect some temporary or fixed effects of alcohol on the brain or of the overall addiction process. In this respect, some of the structural alterations found in AUD appear to regress quickly after cessation of alcohol use.²⁻⁶ Specifically, it was found that high prewithdrawal drinking levels were associated with a faster and more important regression of structural alterations,⁷ suggesting that some brain alterations could result from immediate alcohol neurotoxicity and might thus be merely related to the recent amounts of alcohol used. In contrast, other alterations could be the result of a cumulative exposure to alcohol abuse over the years and thus may be more related to the total duration of heavy alcohol use than to current alcohol use patterns. To our knowledge, no study has ever aimed to differentiate these two types of alterations in the same sample of subjects with AUD. The only study that has previously investigated the link between current drinking levels and structural alterations in subjects with AUD did not find any relation between these factors.³ However, the main methodological limitation of that study was that "recent" alcohol consumption was actually measured as the mean alcohol consumption during the previous year, thus hampering the evaluation of the short-term effects of alcohol on the brain.

Moreover, the most recent longitudinal neuroimaging studies on AUD allow to raise preliminary hypotheses on which brain areas are specifically affected by current alcohol consumption (CAC) or duration of alcohol use disorder (DAD). These studies revealed that there is a partial though substantial structural recovery of almost all brain regions in the months following alcohol withdrawal, except the amygdala.⁶ This suggests that brain alterations in this later region could reflect a cumulative toxicity of alcohol over time, ie, being possibly related to DAD. By contrast, recent alcohol drinking was found particularly associated with reductions of gray matter volumes in frontal regions.^{4,8} Another study conducted in adolescents found that the recent amount of drinking was inversely correlated with cortical thickness in parietal and temporal regions.⁹ These different brain regions could thus be affected by the recent exposure to alcohol, ie, CAC, in subjects with AUD.

To better address the respective impact of CAC and DAD on brain structural alterations, we explored the correlations between these two drinking patterns and the brain volumetric and surface-based parameters within a sample of subjects with AUD, after verifying the relevance of this sample using a direct comparison with healthy controls. We hypothesized that different morphological alterations would be observed with respect to the current level of drinking and the total amount of time of heavy drinking. More specifically, we assumed that alterations in the amygdala could be related with DAD, whereas frontal, temporal, or parietal alterations would be associated with CAC.

2 | MATERIALS AND METHODS

2.1 | Participants

Sixty-six subjects with AUD were recruited from the full-time alcohol detoxification unit of the *Cliniques Universitaires Saint-Luc*, Brussels, Belgium. Participants had abstained from alcohol consumption for 14 to 18 days before being enrolled in the study. The primary inclusion criteria were as follows: (1) meeting the DSM-5 criteria for moderate or severe AUD, based on the clinical assessment of the principal investigator (PDT); (2) being fluent in French; (3) drinking on average more than 500 g of alcohol per week before hospitalization (ie, 50 standard drinks (sds), according to the World Health Organization); and (4) providing written consent for participation before engaging in the experimental procedures.

In addition, 44 control (CON) subjects were also recruited. Controls subjects were matched for gender and age (± 2 years) with the AUD subjects. The inclusion criteria were an alcohol consumption not exceeding the French recommendation for low-risk drinking, ie, more than 14 sds per week for women and more than 21 sds for men.¹⁰ Primary exclusion criteria for both AUD and CON subjects consisted of having no history of addictive, psychiatric, neurological, or physical disorder that could influence brain morphology with the exception of nicotine dependence. In particular, current substance use disorders other than AUD and nicotine dependence, current depressive episode, current anxiety disorder, lifetime psychotic disorder, and lifetime bipolar disorder were assessed by the Principal investigator (PDT), based on the DSM-5 criteria. In addition, diagnostic criteria of cirrhosis and hepatitis C were systematically explored among participants, who were excluded from the study if they met such criteria. Participants could also not have a contraindication for magnetic resonance imaging (MRI).

2.2 | Clinical assessment

For each subject from the AUD and CON groups, the following parameters were collected: age (in years), gender, and tobacco status (ie, current smoker vs current nonsmoker). For subjects in the AUD group, the CAC was defined as the average weekly alcohol consumption during the month prior to detoxification, calculated using the alcohol timeline follow-back method.¹¹ For CON subjects, CAC was calculated based on the reported alcohol consumption during the month preceding the interview. In AUD subjects only, DAD was defined as the total number of years of active heavy drinking, ie, the total periods with an average consumption of more than 14 sds per week for women and no more than 21 sds for men.¹⁰ Periods of abstinence and low-risk drinking were deducted from the total amount.

2.3 | MR data acquisition and processing

3D heavily T1-weighted images were recorded at 3 T (Achieva, Philips Healthcare) with a 32-channel phased array head coil. The 3D sequence consisted of a gradient echo sequence with an inversion

prepulse (Turbo Field Echo) acquired in the sagittal plane using the following parameters: TR/TE/flip angle = 9.1 ms/4.6 ms/8°, 150 slices, slice thickness = 1 mm, in-plane resolution = $0.81 \times 0.95 \text{ mm}^2$ (acquisition) reconstructed in $0.75 \times 0.75 \text{ mm}^2$, FOV = $220 \times 197 \text{ mm}^2$, acquisition matrix = 296×247 (reconstruction 320^2), SENSE factor = 1.5 (parallel imaging). The whole brain was segmented by completing the FreeSurfer image analysis pipeline (<http://surfer.nmr.mgh.harvard.edu/>). The final segmentation (ie, morphometry and surface data) is based on both a subject-independent probabilistic atlas and subject-specific measured values. The atlas is built from a training set comprising a set of 40 participants whose brains (surfaces or volumes) were labeled by hand.¹²⁻¹⁴ After completion of the pipeline, each segmentation was visually inspected and corrected when necessary. Only small skull strips errors were found and corrected before running the data through the pipeline again. Volumetric measures were exported for statistical analysis into the XLSTAT software (<https://www.xlstat.com/en/>). The data were resampled to an average brain template (fsaverage) and smoothed (FWHM = 10 mm) before testing for group differences in the cortical surface using the GUI Qdec, implemented in FreeSurfer.

2.4 | Statistical analyses

Descriptive statistics are presented as the mean $\pm$ standard deviation ($m \pm SD$) for quantitative variables and the number of subjects and percentage (n, %) for categorical variables. Between-group comparisons on sociodemographic and clinical features were conducted using *t* tests for quantitative variables and chi-squared tests or Fisher's exact tests for categorical variables. A direct correlation between CAC and DAD was calculated and presented using Spearman's rank correlation coefficient (ρ).

Between-group MRI comparisons were conducted to assess the volumetric and surface-based features of the AUD group compared with the CON group. Subsequently, MRI analyses were undertaken within the AUD subjects to determine which volumetric and surface-based characteristics were associated with CAC or DAD. Because chronic tobacco smoking also elicits anatomical brain changes that may skew the analyses performed on AUD subjects,¹⁵ we adjusted all MRI analyses for smoking status.

Volumetric analyses were undertaken after an adjustment based on a residual approach.¹⁶ Prior linear regressions were performed using volumetric data of the CON group to model the relationship between each volume of interest and the brain size. For each participant of both groups, residues were subsequently calculated based on the difference between the real volume of the brain structure

TABLE 2A Volumetric comparisons between AUD (n = 66) and CON subjects (n = 44) after adjustment for tobacco status

Volumetric ^a				
Structure	Raw r_p	P value	β_0	P value
Total GM volume	-0.55	<0.0001	-0.46	<0.0001 [*]
Total cortical GM	-0.51	<0.0001	-0.43	<0.0001 [*]
Total cortical WM	-0.48	<0.0001	-0.32	0.001
Total subcortical GM	-0.48	<0.0001	-0.35	<0.0001 [*]
Total ventricular volume	+0.42	<0.0001	+0.36	<0.0001 [*]
L-cerebellar GM	-0.40	<0.0001	-0.42	<0.0001 [*]
R-cerebellar GM	-0.45	<0.0001	-0.41	<0.0001 [*]
L-thalamus	-0.47	<0.0001	-0.40	<0.0001 [*]
R-thalamus	-0.49	<0.0001	-0.41	<0.0001 [*]
L-caudate	-0.17	0.027	-0.16	0.11
R-caudate	-0.16	0.039	-0.10	0.27
L-putamen	-0.34	<0.0001	-0.11	0.04
R-putamen	-0.34	<0.0001	-0.19	0.08
L-pallidum	-0.34	<0.0001	-0.24	0.03
R-pallidum	-0.34	<0.0001	-0.30	0.005
L-accumbens area	-0.18	0.02	-0.11	0.12
R-accumbens area	-0.41	<0.0001	-0.25	0.02
L-hippocampus	-0.44	<0.0001	-0.36	<0.0001 [*]
R-hippocampus	-0.45	<0.0001	-0.40	<0.0001 [*]
L-amygdala	-0.47	<0.0001	-0.35	0.001
R-amygdala	-0.36	<0.0001	-0.23	0.02
L-ventral diencephalon	-0.35	<0.0001	-0.37	<0.0001 [*]
R-ventral diencephalon	-0.43	<0.0001	-0.42	<0.0001 [*]

Abbreviations: AUD, alcohol use disorder; CON, control subjects; GM, gray matter; L, left; R, right; WM, white matter. "^{*}" Significance threshold after Bonferroni correction for multiple comparisons: $P < 0.0004$.

TABLE 1 Clinical characteristics of participants and between-group comparisons

	CON (n = 44)	AUD (n = 66)	P value
Gender, n females, %	19 (43.2)	26 (39.4)	0.69
Age, years, $m \pm SD$ (min-max)	46.9 $\pm$ 9.3 (22-64)	49.0 $\pm$ 10.2 (24-77)	0.23
Tobacco, n smokers, %	8 (18.2)	42 (63.6)	<0.0001
CAC, sd/week, $m \pm SD$ (min-max)	6.3 $\pm$ 6.3 (1-17)	154.7 $\pm$ 88.8 (25-476)	<0.0001
DAD, years, $m \pm SD$ (min-max)	—	13.0 $\pm$ 9.8 (2-47)	NA

Abbreviations: AUD, alcohol use disorder; CAC, current average alcohol consumption; CON, control subjects; DAD, total duration of alcohol use disorder; min-max, minimum-maximum; n: number; *m*, mean; *SD*, standard deviation; sd, standard drink (ie, 10-g ethanol).

TABLE 2B Areas associated with significant surface reductions in AUD ($n = 66$), compared to CON subjects ($n = 66$), after adjustment for tobacco status

Surface Based**						
	Max	Size, mm ²	X	Y	Z	Brain area
1.	6.51	16 909.5	-29.0	-62.6	30.1	L-inferior parietal gyrus
2.	3.57	938	-21.0	16.2	46.6	L-superior frontal gyrus
3.	5.73	1975.3	38.7	-57.4	13.5	R-inferior parietal gyrus
4.	5.28	15 086.7	16.2	-37.1	39.8	R-paracentral
5.	3.87	997.3	42.7	-27.0	35.9	R-supramarginal gyrus

Abbreviations: AUD, alcohol use disorder; CON, control subjects. "**" Correction for multiple comparisons based on the Monte Carlo simulation method ($P < 0.05$).

and the theoretical volume expected according to the subject's brain size based on the linear regression. Between-group volumetric comparisons were thus based on comparing the residues before and after adjustment using ANCOVAs with the tobacco status as an adjustment covariate and with a Bonferroni correction for multiple comparisons. The respective relation between CAC/DAD and volumetric parameters within the AUD group was determined using multivariate linear regressions, after adjustment for age and tobacco status and with a Bonferroni correction for multiple comparisons.

FreeSurfer's Qdec was used to perform a general linear model (GLM) analysis of between-group and within-group comparisons of cortical thickness and gray matter volumes. Between-group analyses were corrected for tobacco status, whereas within-group analyses were corrected for both age and tobacco status. Different regression models were built, using either CAC and DAD independently as a predictor, or simultaneously including them into the same model, the first being used as a predictor and the other one as a nuisance variable, and then conversely. All results were corrected for multiple comparisons using a Monte Carlo simulation ($P < 0.05$).

2.5 | Ethics procedures

The entire study protocol was submitted to and approved by the Bio-medical Ethics Commission of the Université Catholique de Louvain (Belgium).

3 | RESULTS

3.1 | Comparisons between AUD and CON subjects

Descriptive clinical features and bivariate comparisons between the AUD and CON groups are provided in Table 1. Overall, the groups significantly differed only for smoking status and CAC.

Table 2A,B and Figure 1 present the results of the between-group MRI volumetric and surface-based comparisons after adjustment for tobacco status and with a Bonferroni/Monte Carlo correction for multiple comparisons, respectively. Significant volumetric reductions were found in AUD subjects with regard to the total gray matter volume, total cortical and subcortical volumes, total cerebellar gray matter and the volumes of the bilateral thalamus, hippocampus, and diencephalons. By contrast, the total ventricular volume was significantly increased in AUD subjects. Furthermore, after correction for multiple comparisons using the Monte Carlo simulation method ($P < 0.05$), the between-group surface-based comparisons showed reduced cortical thickness in AUD subjects for the bilateral inferior parietal cortices, left superior frontal cortex, and right paracentral and supramarginal gyri.

3.2 | Influence of drinking patterns on brain structural alterations within the AUD subjects

The CAC and DAD scores within subjects of the AUD group were significantly correlated ($\rho = 0.25$, $P < 0.0001$). Tables 3 and 4 and Figures 2

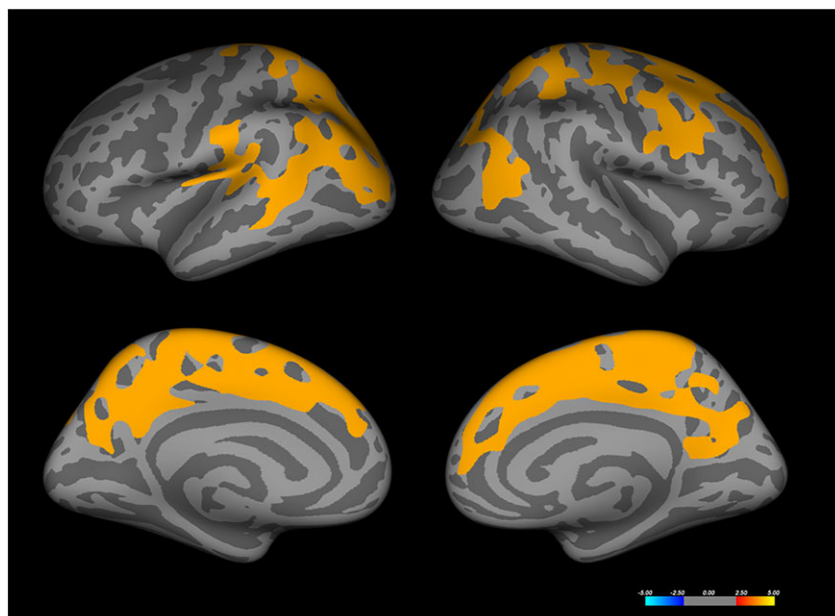


FIGURE 1 Brain areas showing significantly larger cortical thickness in control subjects compared with subjects with alcohol use disorder. Correction for multiple comparisons using Monte Carlo simulation ($P < 0.05$), after adjustment for tobacco status

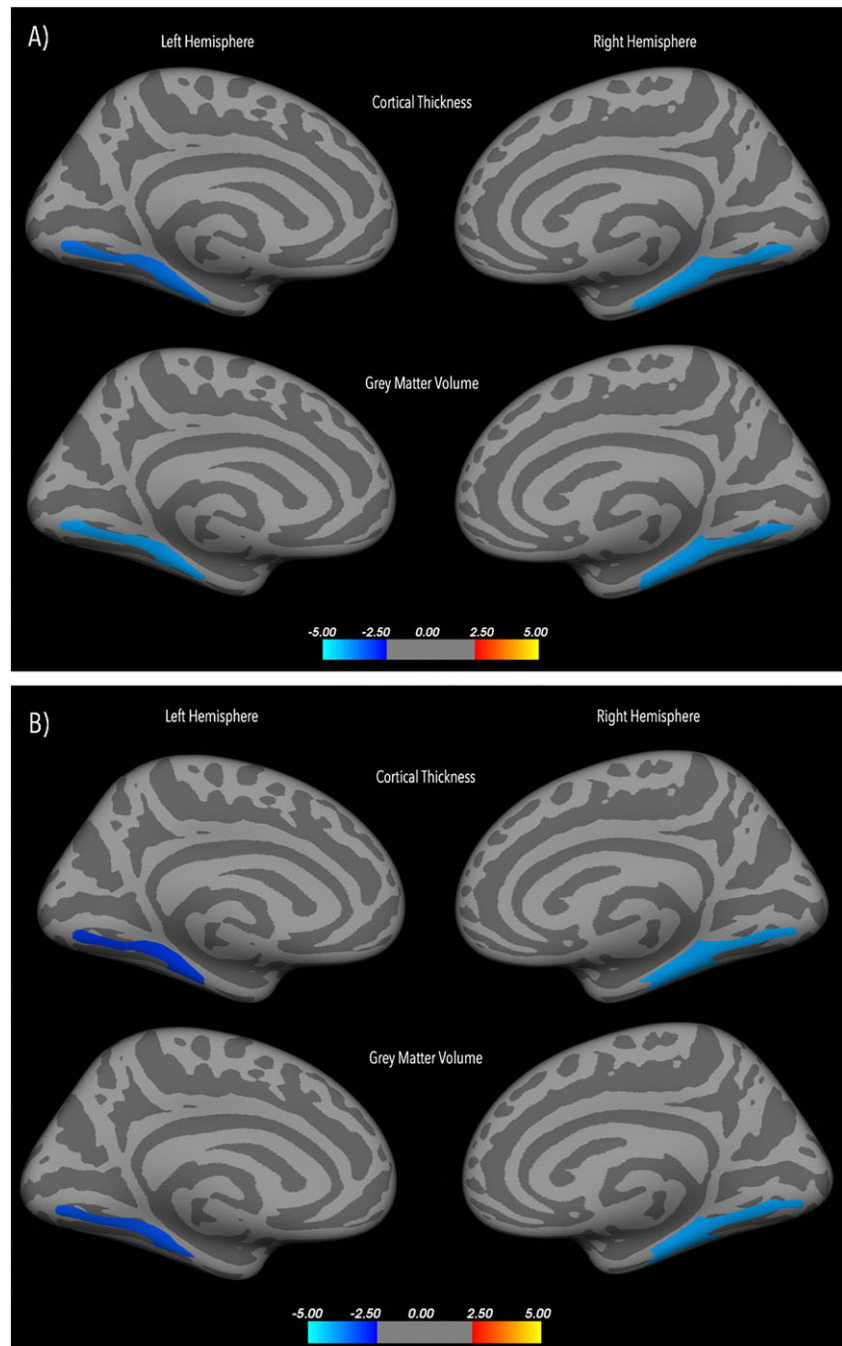


FIGURE 2 Results of the within-alcohol use disorder analyses showing the temporal brain areas in which cortical thickness or gray matter volume was found negatively correlated with the current level of alcohol consumption. Correction for multiple comparisons using Monte Carlo simulation ($P < 0.05$), after adjustment for age and tobacco status. A, No adjustment for duration for alcohol dependence; B, adjustment for duration for alcohol dependence

and 3 display the brain structures for which volume or cortical thickness was significantly associated with the CAC and DAD parameters, respectively, within the AUD subjects.

Adjusted volumetric analyses revealed that CAC was negatively correlated with volumetric reductions in the bilateral putamen ($P = 0.003$ for the left putamen and $P = 0.02$ for the right putamen), but these correlations did not reach significance after Bonferroni correction. Similarly, DAD was negatively correlated with the total gray matter volume ($P = 0.03$) and total cortical gray matter volume ($P = 0.02$), as well as the volume of the right diencephalon ($P = 0.009$). However, none of these correlations reached the significance threshold after applying a Bonferroni correction.

Regarding the surface-based analyses and after correcting for multiple comparisons using the Monte Carlo simulation method ($P < 0.05$), CAC was significantly associated with reduced cortical thickness in the left fusiform gyrus and right parahippocampal gyrus (Figure 2A and Table 3A,B). A very similar result was found for gray matter volume analyses (Figure 2A and Table 3A,B). The use of DAD as a nuisance variable did not change these overall results (Figure 2B and Table 3A,B).

By contrast, DAD was significantly associated with reduced cortical thickness in the left temporal pole and right superior temporal gyrus (see Figure 3A and Table 4A,B). After integration of CAC in the regression models, only the left temporal pole survived in the analyses (Figure 3B and Table 4A,B).

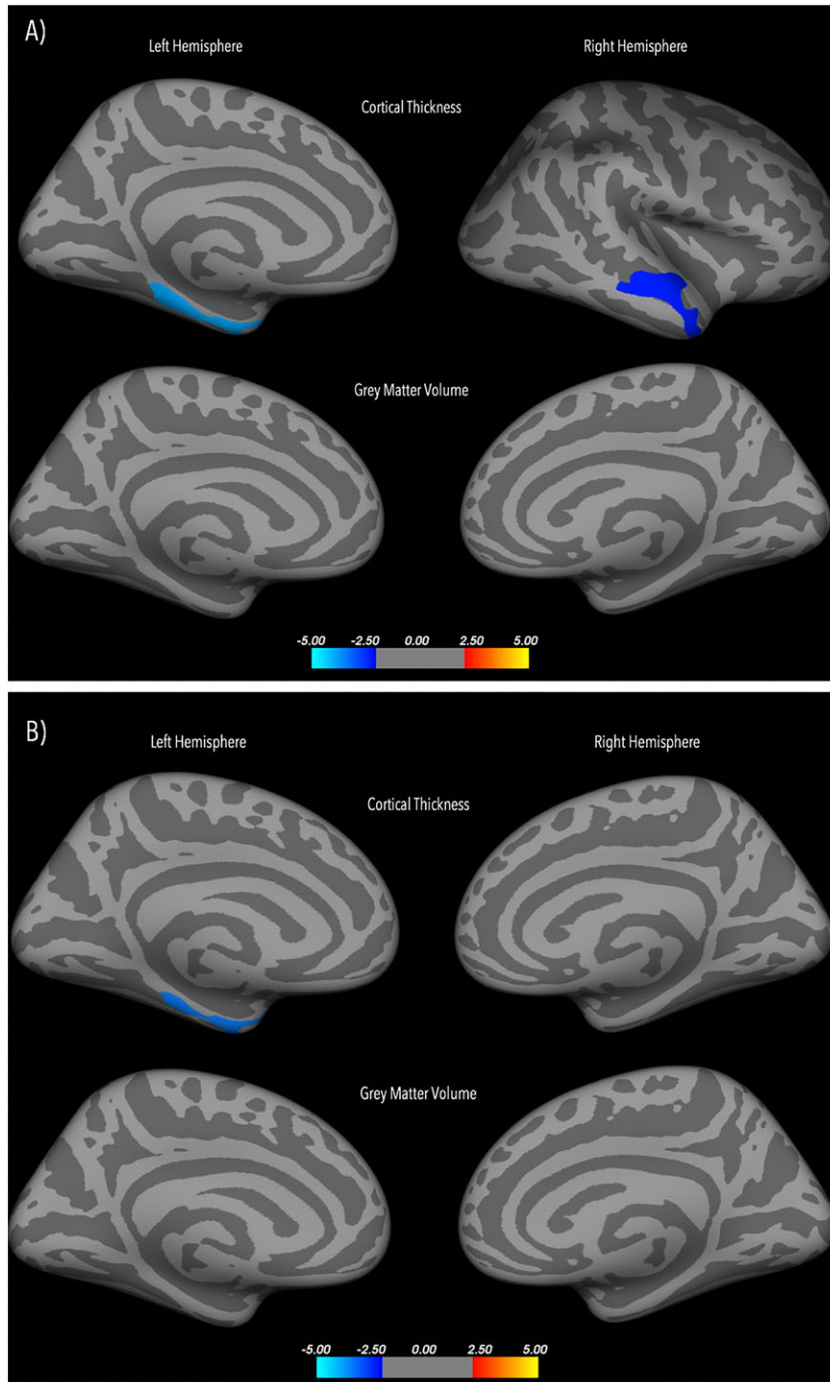


FIGURE 3 Results of the within-alcohol use disorder analyses showing the temporal brain areas in which cortical thickness or grey matter volume was found negatively correlated with the duration of alcohol dependence. Correction for multiple comparisons using Monte Carlo simulation ($P < 0.05$), after adjustment for age and tobacco status. (A) No adjustment for current level of alcohol consumption; (B) adjustment for current level of alcohol consumption

4 | DISCUSSION

The aim of this study was to explore which morphological alterations were respectively associated with DAD or CAC among subjects with AUD. Before that, between-group comparisons were conducted to reproduce previous results comparing control subjects with patients with AUD and thus to support the reliability of our AUD group before conducting within-group analyses. AUD subjects exhibited significant reductions in total gray matter volume, total cortical and subcortical volumes, total cerebellar gray matter and in the volumes of the bilateral thalamus, hippocampus, cerebellum, and diencephalons, as well

as an increase in the total ventricular volume. Moreover, between-group surface-based comparisons found a reduced cortical thickness in AUD subjects for the bilateral inferior parietal cortices, left superior frontal cortex, and right paracentral and supramarginal gyri. Overall, these findings are in line with previous morphological comparisons between subjects with AUD and controls, though we did not find any difference in white matter volumes, which has been consistently reported.^{1,17}

The strongest results of the study pertained to the surface-based analyses, in particular for CAC. Using Monte Carlo simulation to control for multiple comparisons, we found that CAC was significantly

TABLE 3A Volumetric brain areas associated with the current alcohol consumption within the AUD subjects (n = 66)

Volumetric Analyses				
	Raw r_p	P value	β_0	P value
Total GM volume	-0.17	0.18	-0.16	0.11
Total cortical GM	-0.15	0.23	-0.14	0.18
Total cortical WM	-0.16	0.21	-0.15	0.20
Total subcortical GM	-0.18	0.15	-0.19	0.09
Total ventricular volume	+0.12	0.35	+0.12	0.40
L-cerebellar GM	-0.13	0.29	-0.15	0.21
R-cerebellar GM	-0.16	0.48	-0.19	0.13
L-thalamus	-0.10	0.41	-0.07	0.56
R-thalamus	-0.11	0.29	-0.20	0.12
L-caudate	-0.11	0.38	-0.14	0.25
R-caudate	-0.21	0.10	-0.11	0.08
L-putamen	-0.31	0.01	-0.31	0.003
R-putamen	-0.16	0.21	-0.23	0.02
L-pallidum	-0.03	0.82	+0.01	0.95
R-pallidum	-0.16	0.21	-0.17	0.12
L-accumbens area	-0.18	0.15	-0.16	0.17
R-accumbens area	-0.12	0.35	-0.02	0.42
L-hippocampus	-0.06	0.62	-0.03	0.79
R-hippocampus	-0.20	0.19	-0.14	0.23
L-amygdala	+0.07	0.21	+0.11	0.35
R-amygdala	-0.05	0.67	+0.01	0.90
L-ventral diencephalon	-0.08	0.60	-0.08	0.51
R-ventral diencephalon	-0.18	0.15	-0.20	0.11

Abbreviations: AUD, alcohol use disorder; DAD, duration of alcohol use disorder; GM, gray matter; L, left; R, right; r_p , Pearson correlation coefficient; β_0 , normalized coefficient (linear regression); WM, white matter. Significance threshold after Bonferroni correction for multiple comparisons: $P < 0.0004$. In bold are highlighted the P values $P < 0.05$.

associated with reduced cortical thickness, as well as reduced gray matter volume, in a band-shape area corresponding to the left fusiform gyrus and the right parahippocampal cortex (see Table 3A,B and Figure 2). These areas were almost symmetrical, and they were very similar in cortical thickness and gray matter volume analyses. Moreover, they largely persisted after adjustment for DAD (Figure 2B). We thus consider that this is a robust finding. For DAD, results were somewhat less straightforward. The areas associated with DAD in cortical thickness analyses were slightly more ventral and involved the left temporal pole and the superior temporal gyrus (Table 3A,B and Figures 3). Right and left identified areas were not symmetrical, and they were not found in gray matter volume analyses. Last, the right area did not survive after adjustment for CAC.

The substantial overlap between the areas respectively associated with CAC and DAD may be partially explained by the significant correlation between the two parameters. This is logical insofar as

TABLE 3B Surface-based brain areas associated with the current alcohol consumption within the AUD subjects (n = 66)

Surface-based Analyses						
	Max	Size, mm ²	X	Y	Z	Brain Area
Cortical thickness analyses (non-adjusted for DAD)						
1.	-3.54	1475.6	-35.1	-23.3	-22.8	L-fusiform gyrus
2.	-4.00	1709.0	31.0	-41.1	-9.0	R-parahippocampal gyrus
Grey matter volume analyses (non-adjusted for DAD)						
1.	-4.00	1365.6	-7.7	-79.7	-2.0	L-lingual gyrus
2.	-4.00	1573.8	31.0	-41.1	-9.0	R-parahippocampal gyrus
Cortical thickness analyses (adjusted for DAD)						
1.	-2.75	1289.2	-35.3	-40.6	-11.2	L-fusiform gyrus
2.	-6.05	1701.0	31.4	-34.0	-10.5	R-parahippocampal gyrus
Grey matter volume analyses (adjusted for DAD)						
1.	-3.05	1157.3	-7.7	-79.7	-2.0	L-lingual gyrus
2.	-4.00	1742.7	31.0	-41.1	-9.0	R-parahippocampal gyrus

Abbreviations: AUD, alcohol use disorder; DAD, duration of alcohol use disorder; L, left; R, right. Correction for multiple comparisons based on the Monte Carlo simulation method ($P < 0.05$), after adjustment for age and tobacco.

individuals with longer drinking histories are more likely to drink more on average, including in the month preceding the study.

Based on previous literature, several candidate zones were initially hypothesized to be associated with either DAD (ie, the amygdala) or CAC (ie, the frontal, temporal, or parietal cortices). In the end, we found for both parameters that only the temporal lobe appeared as a vulnerability zone. While the parahippocampal cortex is involved in visuospatial processing, episodic memory, and contextual associations,¹⁸ the fusiform gyrus is involved in other memory processes, including memory for people and their relationships and memory for social language and social behaviors.¹⁹ The finding that CAC was correlated with reduced cortical thickness and reduced gray matter volume in brain areas underlying episodic and semantic memory is of interest when considering neuropsychological studies showing that the memory impairments classically related to AUD strongly regress following abstinence.^{20,21} Indeed, the structural changes observed in memory-related brain regions, as they appear mostly related to recent alcohol consumption, might be those with faster recovery rates following alcohol use cessation, allowing an efficient recovery of memory abilities.

Regarding volumetric results, after applying a Bonferroni correction, no specific volumetric parameter was associated with either CAC or DAD. When the Bonferroni correction was not applied ($P < 0.05$), DAD was significantly associated with reduced total gray matter and total cortical gray matter volumes. This may suggest that the global gray matter loss observed in AUD is more a consequence of the cumulative toxicity of alcohol over time (time effect) than of an immediate effect of the current drinking level (dose effect). Moreover, reductions in the bilateral Putamen were associated with CAC, whereas a reduction of the bilateral diencephalons tends to be

TABLE 4A Volumetric brain areas associated with the duration of alcohol use disorder within the AUD subjects (n = 66)

Volumetric Analyses				
	Raw r_p	P value	β_0	P value
Total GM volume	-0.45	<0.0001*	-0.23	0.03
Total cortical GM	-0.46	<0.0001*	-0.25	0.02
Total cortical WM	-0.37	0.002	-0.21	0.09
Total subcortical GM	-0.33	0.007	-0.15	0.20
Total ventricular volume	+0.21	0.09	0.08	0.58
L-cerebellar GM	-0.25	0.04	-0.11	0.38
R-cerebellar GM	-0.22	0.07	-0.10	0.45
L-thalamus	-0.29	0.02	-0.10	0.42
R-thalamus	-0.33	0.007	-0.11	0.34
L-caudate	-0.26	0.04	-0.13	0.31
R-caudate	-0.28	0.02	-0.10	0.45
L-putamen	-0.41	0.001	-0.13	0.25
R-putamen	-0.36	0.003	-0.14	0.21
L-pallidum	-0.31	0.01	-0.12	0.31
R-pallidum	-0.30	0.01	-0.11	0.35
L-accumbens area	-0.28	0.02	-0.11	0.38
R-accumbens area	-0.25	0.04	-0.07	0.58
L-hippocampus	-0.22	0.08	-0.06	0.10
R-hippocampus	-0.22	0.08	-0.03	0.79
L-amygdala	0.09	0.50	-0.10	0.45
R-amygdala	-0.29	0.02	-0.10	0.43
L-ventral diencephalon	-0.32	0.008	-0.23	0.08
R-ventral diencephalon	-0.41	0.001	-0.34	0.009

Abbreviations: AUD, alcohol use disorder; CAC, current level of alcohol consumption; GM, gray matter; L, left; R, right; r_p , Pearson correlation coefficient; β_0 , normalized coefficient (linear regression); WM, white matter. Significance threshold after Bonferroni correction for multiple comparisons: $P < 0.0004$. In bold are highlighted the P values $P < 0.05$.

associated with DAD. These findings should be interpreted with caution, since the associations observed do not reach the Bonferroni significance threshold. However, they deserve discussion, as these preliminary results might be confirmed in future studies involving more subjects. Moreover, some previous data are in line with these findings; they showed that putamen functioning was directly and specifically affected by DAD and might underlie impairments in altered response inhibition and impulse control.²²⁻²⁴ It is more difficult to interpret the possible association found between CAC and reduced size of the bilateral diencephalon. Interestingly, another recent study found that the functioning of the bilateral ventral tegmental areas (VTAs) was associated with relapse in subjects with AUD.²⁵ As CAC is known to be a significant contributor of the risk of relapse in AUD,²⁶ recent levels of alcohol use could morphologically affect some of the reward structures in the brain, especially the VTAs, thereby affecting the risk of relapse. However, further studies are needed to

TABLE 4B Volumetric brain areas associated with the duration of alcohol use disorder within the AUD subjects (n = 66)

Surface-based Analyses						
	Max	Size, mm ²	X	Y	Z	Brain Area
Cortical thickness analyses (non-adjusted for CAC)						
1.	-4.00	1536.7	-28.2	5.8	-34.2	L-temporal pole
2.	-2.37	1214.4	47.5	5.0	-27.2	R-superior temporal gyrus
Grey matter volume analyses (non-adjusted for CAC)						
No significant result						
Cortical thickness analyses (adjusted for CAC)						
1.	-3.52	1476.0	-28.2	5.8	-34.2	L-temporal pole
Grey matter volume analyses (adjusted for CAC)						
No significant result						

Abbreviations: AUD, alcohol use disorder; CAC, current level of alcohol consumption; L, left; R, right. Correction for multiple comparisons based on the Monte Carlo simulation method ($P < 0.05$), after adjustment for age and tobacco.

confirm this preliminary finding and to assess if structural modifications in the mesencephalon are reversible with reduced CAC.

This study has several limitations that should be acknowledged. Analyses were not adjusted for gender, but a recent study found that there was no sex-related effect regarding the morphological alterations within AUD subjects, while age should be taken into account.²⁷ Another limitation is that differentiating the respective effects of CAC and DAD would have benefited from a design based on repeated MRI examinations, which could have allowed measurement of the reversibility of some of the brain alterations. By contrast, the present study was cross-sectional. Finally, DAD was calculated retrospectively, with the total number of years of heavy drinking as a proxy. We acknowledge that there may be a gap between the total duration of heavy drinking and the total duration of DAD, but it was impossible in practice to retrospectively assess the criteria for AUD.

In conclusion, this study found evidence of specific brain morphological alterations for CAC, and to a lesser extent, for DAD, in subjects with AUD, in partially overlapping areas of reduced cortical thickness in the bilateral temporal lobes. Future investigations are needed to determine the extent to which these specific alterations evolve after prolonged abstinence and if they are associated with neuropsychological impairments.

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