Effect of chronic alcohol consumption on brain structure in males with alcohol use disorder without a familiar history of alcoholism.

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Abstract

Structural brain damages caused by chronic alcohol consumption have been extensively reported. However, the neuroimaging findings in people with alcohol use disorder (AUD) are relatively inconsistent. This inconsistency may be due to the influence of different clinical and sociodemographic variables that are not always considered, such as the presence of a family history of alcoholism (FHA). The main aim of this research is to study the gray (GM) and white matter (WM) volumes in male participants with AUD without FHA compared to healthy control males (HC) without FHA. For this study, we included 19 participants with AUD and 18 HC. T1-weighted images were acquired with a General Electric Signa Exite 1.5 Tesla scanner. GM and WM tissues were calculated using Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL). All analyses were controlled for age and total brain volume. The statistical threshold was calculated with AlphaSim and further adjusted to account for the non-isotropic smoothness of structural images, according to Hayasaka et al. (2004). The obtained main results showed that, relative to the HC group, the participants with AUD had significantly lower GM in several brain structures, reflecting relatively purely the effects of chronic alcohol intake on brain volume. GM structure integrity is relevant for the efficient functioning of low and high-order cognitive processes used in everyday life, and its damage seems to be related to the severity, intensity, and chronicity of the AUD. As such, it becomes relevant to assess and follow brain structural changes through the dependence course.

Keywords: Alcohol use disorder; Brain structure; Gray matter; Magnetic resonance imaging; Family history of alcoholism.

Introduction

Alcohol is a substance consumed worldwide, and in a certain number of cases, its consumption can become pathological, leading to the development of alcohol use disorder (AUD). This disorder has become a public health problem that carries a range of costs to individuals, families, and societies (Hammer et al., 2018; Rehm et al., 2017, 2009). A detailed understanding of the consequences of chronic alcohol consumption on the brain is essential to reduce these costs.

In recent years there have been significant technological advances in brain imaging techniques. Thanks to these advances, we can better understand the effects of alcohol consumption and dependence on the brain at a structural level. Previous studies that have used these techniques in the study of alcohol dependence show in general lower gray (GM) and white matter (WM) in different brain areas (Dupuy and Chanraud, 2016; Yang et al., 2016). On the one hand, previous literature reported that people with AUD showed a reduction of GM volume in several areas, such as the frontal lobe, hippocampus, posterior cingulum, insular cortex, thalamus, amygdala, and cerebellum compared with healthy controls (HC) (Dupuy and Chanraud, 2016; Xiao et al., 2015; Yang et al., 2016). On the other hand, other studies also reported that people with AUD showed a reduction of WM volume in different regions, such as the paraventricular area, pons, cerebellum, corpus callosum, frontotemporal area, and hippocampus (Dupuy and Chanraud, 2016). These regions are involved in different functions that had been found to be altered in people who have developed an AUD, such as reward processing, behavioral learning and automatization, interoceptive integration, consideration of subjective values and reward expectations, multi-cue associative learning, representation/maintenance of goals during motivated behavior, and cognitive regulation (Koob and Volkow, 2010; Zilverstand et al., 2018). However, as Yang et al. (2016) suggested, although structural brain alterations caused by long-term and excessive alcohol consumption have long been extensively reported, the structural neuroimaging findings in people with AUD are relatively inconsistent. This is because the structures found to be altered vary from study to study (Brooks et al., 2014; Chanraud et al., 2009; Demirakca et al., 2011; Grodin et al., 2013; Shim et al., 2019; van Holst et al., 2012). In fact, this inconsistency appears even among meta-analyses (Xiao et al., 2015; Yang et al., 2016).

The inconsistency between studies may be due to the influence of different variables that had not always been considered on these studies. One of these variables is the presence of a family

history of alcoholism (FHA). AUD has an important hereditary component at both biological and psychosocial levels (Bratek et al., 2013; Enoch, 2003; Jacob and Johnson, 1997; Schuckit, 2000), and several studies have reported that its presence is related to brain tissue alterations both in healthy and clinical samples (Filippi et al., 2019; Gilman et al., 2007; Sjoerds et al., 2013). For example, Filippi et al. (2019) reported that HC with FHA showed smaller GM volumes in the frontal, cingulate, bilateral nucleus accumbens, and right insula than HC without FHA. Likewise, Gilman et al. (2007) found that people with AUD with FHA had significantly smaller intracranial volumes than those with AUD without FHA. These examples show that the inclusion of participants with FHA in an undifferentiated form adds a possible interaction between chronic alcohol consumption and hereditary components of AUD on the brain. Therefore, a way of reducing this confounding interaction would be to investigate brain structural changes related to chronic alcohol consumption in persons with AUD without FHA. Besides, the reduction of this confounding interaction also allows us to characterize better the relationship between the clinical characteristics and the structural integrity of the brain, such as the relationship between the AUD severity and the brain volume (Paul et al., 2008; Pfefferbaum et al., 1998; Thayer et al., 2016).

For this reason, our main aim is to study the GM/WM volumes in male participants with AUD without FHA compared to HC without FHA. Our second aim is to explore the relationship between the clinical characteristics of the AUD participants and GM/WM volumes. We expect to find that people with AUD will have lower GM/WM volume in different brain regions than controls, as well as significant relationships between clinical characteristics of people with AUD and brain volumes.

Methodology

Participants

The sample of this study was composed of twenty-nine males in abstinence (ALC) who met the diagnostic criteria for AUD described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) (47.6 ± 8.9 years old) and nineteen HC males (43.3 ± 6.3 years old). All participants with AUD were recruited into the therapeutic program for alcohol-related problems at the Hospital 12 de Octubre in Madrid (Spain). Considering the fact that a reduced number of women attend treatment for AUD and the differences in the pathophysiology of alcohol consumption between men and women (Dettling et al., 2008), we decided to include only males in this study,

controlling the sex effect. After recruitment and the signing of the informed consent, data collection was carried out in two sessions. In the first session, we conducted a semi-structured interview to obtain sociodemographic and clinical information. In addition, the Alcohol Dependence Intensity Scale (ADIS) was administered to assess the intensity of alcohol dependence (Rubio et al., 1998). This scale provides information about the dependence intensity, ranging from mild to moderate and severe intensity. In the second session, we obtained structural magnetic resonance imaging (MRI) of all participants. The exclusion criteria used in this study were the same as those used in Sion et al. (2020), in addition to the presence of FHA. Every effort was made to ensure that all participants had a negative FHA up to the second degree. Due to this, a total of 10 participants with AUD and one HC were excluded from the study because they had FHA. The study protocol was designed under the principles set out in the Declaration of Helsinki, which has also been reviewed and approved following the ethical standards of the Instituto de Investigación Biomédica Hospital 12 de Octubre (TEC2012-38453-C04-04) ethics committee.

Structural MRI acquisition

The technical parameters used for the structural images acquisition were the same as those used in Sion et al. (2020). These images were acquired using a General Electric Signa Exite 1.5 Tesla scanner located at the Hospital 12 de Octubre. An eight-channel coil (head-Beckham) was used, and images were acquired in the sagittal plane (Parameters: SAGITAL 3D FSPGR: TE: min full/Prep time: 600 ms, FA: 8°, BW: 15.63 Hz, Matrix: 256x256, NEX: 1; FOV: 25.6 cm, Thickness: 1 mm, Locs/slabs: 90, 90 slices, Scan time: 9:36 min).

Structural image processing

The structural image processing protocol carried out for this study was similar to the one used by Esteban-Cornejo et al. (2017). We used the Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab R2019b (The MathWorks, Inc, Natick, MA) to pre-process the obtained structural images. Before tissue classification, we checked each image for acquisition artifacts and alignment along the horizontal anterior commissure and posterior commissure plane. The steps followed for the pre-processing of the images were as follows. First, using the latest segmentation algorithm implemented in SPM12, we segmented T1- weighted structural images of each participant into GM tissue, WM tissue, and cerebrospinal fluid (Ashburner and Friston, 2005). Second, we created a customized template using segmented GM, WM, and cerebrospinal fluid

employing the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) (Ashburner, 2007). DARTEL estimates the best set of smooth deformations from every participant's tissue to their common average and reiterates the process until convergence. The obtained images were spatially normalized to the Montreal Neurological Institute (MNI) space with an analog transformation to create the DARTEL template. Subsequently, each participant's segmented images were normalized to the DARTEL template via nonlinear transformation. After the normalization process, the images were modulated with Jacobian determinants derived from the spatial normalization to perform a volume change correction (Ashburner and Friston, 2000). Finally, we performed a smoothing of the volumetric images by convolving them with an isotropic Gaussian kernel of 8 mm full-width at half-maximum (FWHM).

Statistical analysis

Between-group differences in sociodemographic, clinical, and self-assessment outcomes were compared using Student's t-test for independent samples and Chi-square test for quantitative and nominal variables, respectively. Statistical analyses of imaging data were performed in two ways. On the one hand, between-group comparisons were performed using a whole-brain voxel-wise two-sample t-test implemented in SPM12 adjusted for age and total brain volume (TBV; cm^3). TBV was calculated by adding the GM, WM, and cerebrospinal fluid volumes derived from non-normalized segmented images. On the other hand, the association between clinical/self-assessment variables obtained from the AUD group (age of first consumption, pathological consumption duration, abstinence time, and total score of the ADIS scale) and GM/WM volume was computed using a whole-brain voxel-wise one-sample t-test implemented in SPM12. These analyses were also adjusted for age and TBV. Besides, we extracted the eigenvalues from the peak coordinates of each cluster of significant results. To know the magnitude of the association, we used those eigenvalues to perform partial correlations between the mentioned variables adjusted for age and TBV with the software SPSS 25.

The AlphaSim method (implemented in the Resting-State fMRI Data Analysis Toolkit toolbox, RESTplus) was used to calculate the statistical threshold in the imaging analysis (Song et al., 2011). Parameters were defined as follows: cluster connection radius (rmm) = 5 mm and the actual smoothness of the data after model estimation, incorporating a gray mask volume of 405.970 voxels or a white mask volume of 279.662 voxels. We also indicated in the results the

voxel-level alpha significance (threshold, $p < 0.001$ uncorrected) and the appropriate cluster size to control for multiple comparisons in each analysis. The clusters extents were also adjusted to account for the non-isotropic smoothness of the structural images, according to Hayasaka et al. (2004).

Results

Sociodemographic, clinical, and self-assessment information

The study's final sample included 19 participants with AUD and 18 HC, without significant age or educational level differences. Participants with AUD had a mean age of 47.89 (9.21) years old, whereas HC had a mean age of 43.33 (6.46) years old ($t = 1.735$; $p = 0.092$). In terms of the educational level, nine participants with AUD and three HC had primary studies, eight participants with AUD and fourteen HC had secondary studies, and two participants with AUD and one HC presented university studies ($X^2 = 4.946$; $p = 0.084$).

HC participants mostly had an occasional drinking pattern (specific celebrations) (61.1%), followed by rare to non-drinking (27.8%), and frequent social drinking (on weekends and holidays) (11.1%). 50% of HC participants were smokers (average daily pattern: 11.11 ± 7.42 cigarettes], 16.7% were ex-smokers, and 33.3% were non-smokers. For participants with AUD, clinical and other substance use characteristics are shown in Table 1. Regarding self-assessment information about alcohol dependence intensity, both groups were significantly different on the ADIS scale scores [ALC: 30.10 ± 16.23; HC: 1.33 ± 2.33; $t = 7.643$; $p < 0.001$]. Participants with AUD showed moderate/severe intensity symptoms of alcohol dependence (Rubio et al., 1998; Sion et al., 2020).

Table 1. Patterns of substance use in participants with AUD.

Measure	M (SD)/Frequency percentage (%)
Initial age of consumption	16.37 (4.76)
Pathological consumption duration (years)	20.52 (13.25)
Abstinence time (months)	3.89 (2.74)
Tobacco	
Yes	89.5%
Cigarettes/day	18.89 (22.78)
History of other drug consumption	
Cannabis	21.1%
Cocaine	15.8%

Mean (M); Standard Deviation (SD)

Neuroimaging results

Between-group differences. Participants with AUD, relative to HC, demonstrated significantly less GM volume in the superior temporal gyrus, parahippocampal gyrus, uncus, insula, caudate, putamen, amygdala, anterior cingulate cortex, thalamus, claustrum, and inferior frontal gyrus (Table 2 and Figure 1). Regarding WM volumes, we did not find significant differences between groups.

Correlational results. The years of pathological alcohol consumption of the participants with AUD correlated inversely with the GM volume of the middle frontal gyrus [coordinates (x,y,z) = 38, 45, 27; k_E = 1070; t = 6.08; r = -0.855; $p < 0.001$; AlphaSim at $p < 0.001$ with k_E = 732 voxels] (Figure 2). Regarding de association between self-assessment information about alcohol dependence intensity, the scores of the ADIS reported by individuals with AUD correlated inversely with the GM volumes of different brain regions shown in table 3 and represented in figure 3.

Table 2. Brain regions that showed significant differences in GM volumes between groups. Individuals with AUD had lower GM volumes than healthy controls.

	Brain region (hemisphere)	x, y, z	k_E	Peak t value
ALC < HC	Superior Temporal Gyrus (l)	-45, 3, -3	8882*	4.71
	Parahippocampal Gyrus (l)	-15, 1.5, -16.5	8882*	4.66
	Parahippocampal Gyrus (r)	16.5, -3, -15	8882*	4.15
	Uncus (r)	25.5, 4.5, -28.5	8882*	4.00
	Insula (l)	-40.5, 10.5, 1.5	8882*	4.36
	Insula (r)	38, -3, -9	8882*	5.08
	Caudate (l)	-8, 9, -5	8882*	4.24
	Caudate (r)	6, 18, 0	8882*	4.61
	Putamen (l)	-24, -6, -6	8882*	3.75
	Amygdala (l)	-18, -4.5, -21	8882*	4.51
	Amygdala (r)	28.5, -1.5, -21	8882*	4.04
	Anterior Cingulate (r)	3, 6, -5	8882*	4.84
	Thalamus (r)	4.5, -3, 3	8882*	4.21
	Claustrum (l)	-34.5, -3, -4.5	8882*	4.35
	Inferior Frontal Gyrus (l)	-49.5, 16.5, 1.5	8882*	4.35

All contrasts were thresholded using AlphaSim at $p < 0.001$ with $k_E = 644$ voxels. x,y,z = MNI peak coordinates; k_E, cluster extent in voxels; ALC, group of participants with AUD; HC, group of healthy control participants; l, left; r, right; *part of a larger cluster.

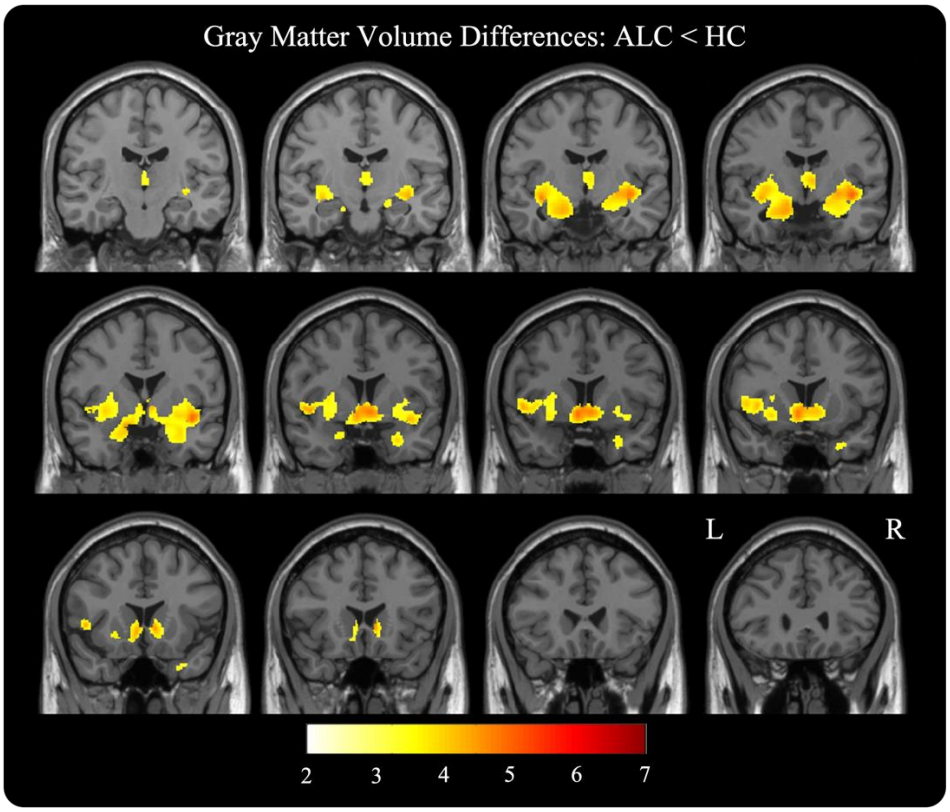

Figure 1. Brain regions representation showing significant differences in the comparison between ALC and HC groups. The colors in the image represent the obtained t-values. L, left hemisphere; R, right hemisphere.

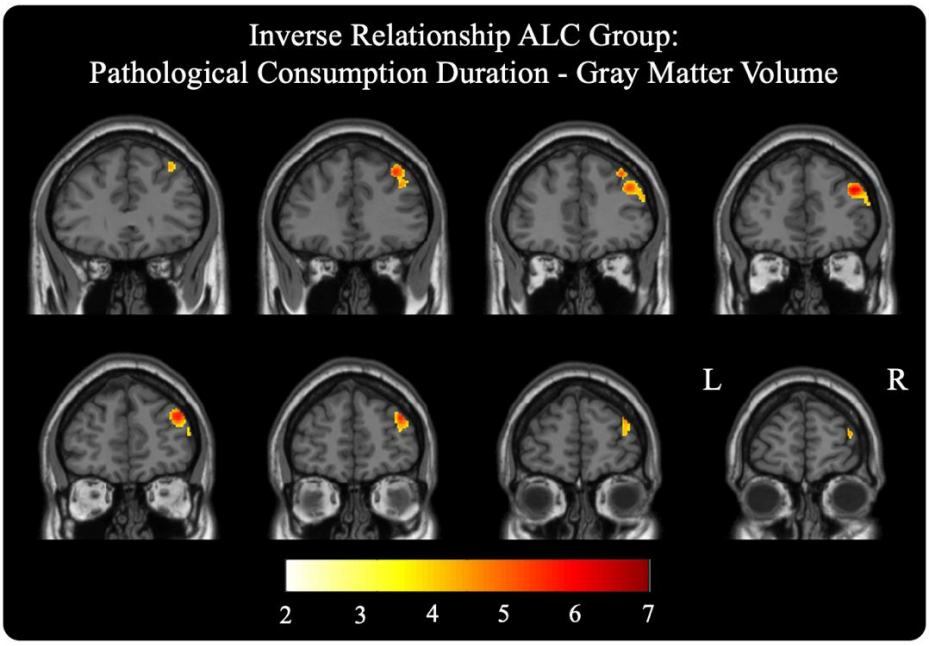

Figure 2. Brain regions representation showing a significant relationship between pathological alcohol consumption duration and GM volumes. The colors in the image represent the obtained t-values. L, left hemisphere; R, right hemisphere.

Table 3. Brain regions of the ALC group showing significant relationships between the scores of the ADIS scale and GM volumes.

ADIS Scale					
Brain region (hemisphere)	x, y, z	k_E	Peak t value	r	p
Superior Frontal Gyrus (l)	-14, 51, 30	1562*	6.94	-0.874	<0.001
Middle Frontal Gyrus (r)	44, 44, -3	892*	4.46	-0.746	0.001
Medial Frontal Gyrus (l)	-4.5, 49.5, 48	1562*	4.24	-0.729	0.001
Inferior Frontal Gyrus (r)	50, 23, 0	892*	6.56	-0.826	<0.001
Paracentral Lobule (r)	10.5, -46.5, 64.5	5978*	3.88	-0.725	0.001
Middle Temporal Gyrus (r)	41, -3, -41	1209*	5.67	-0.818	<0.001
Inferior Temporal Gyrus (r)	54, -49.5, -19.5	5978*	6.12	-0.826	<0.001
Parahippocampal Gyrus (r)	35, -14, -30	1209*	4.30	-0.742	0.001
Uncus (r)	30, 0, -39	1209*	4.30	-0.736	0.001
Lingual Gyrus (r)	15, -90, -15	5978*	6.28	-0.837	<0.001
Cuneus (l)	-5, -87, 32	5978*	6.18	-0.837	<0.001
Cuneus (r)	1.5, -91.5, 12	5978*	4.97	-0.778	<0.001
Precuneus (l)	-3, -79.5, 40.5	5978*	4.81	-0.785	<0.001
Precuneus (r)	3, -64.5, 60	5978*	4.81	-0795	<0.001
Middle Occipital Gyrus (r)	50, -65, -12	5978*	6.56	-0.866	<0.001
Fusiform Gyrus (r)	40.5, -82.5, -19.5	5978*	4.65	-0.758	<0.001

Posterior Cerebellum Lobule (l)	-39, -50, -57	678*	5.58	-0.803	<0.001

All contrasts were thresholded using AlphaSim at $p < 0.001$ with $k_E = 674$ for the inverse relationship between the scores of the ADIS scale and GM volumes. x,y,z = MNI peak coordinates; k_E, cluster extent in voxels; GM, gray matter; l, left; r, right; *part of a larger cluster.

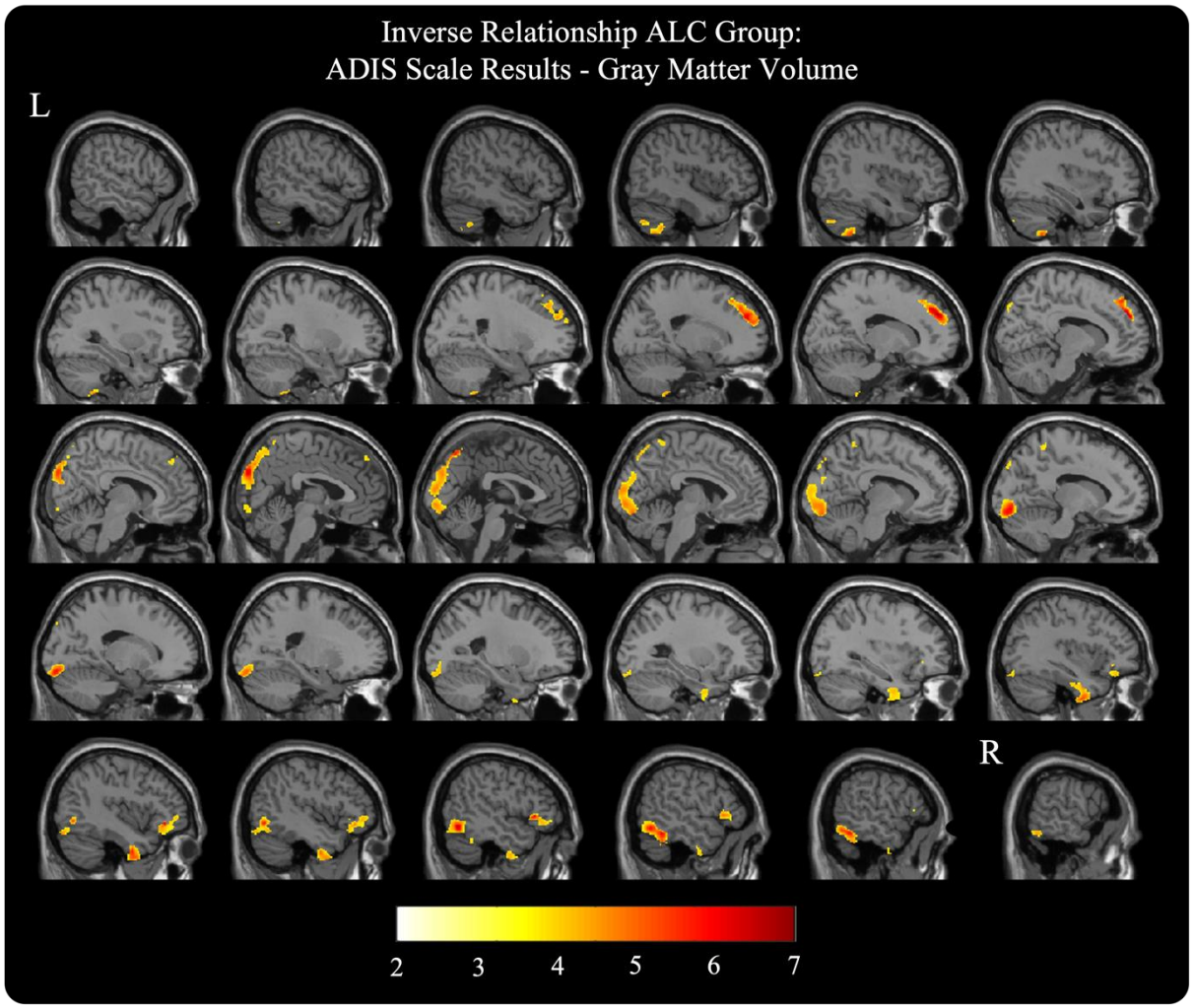

Figure 3. Brain regions representation showing significant relationships between the scores of the ADIS scale and GM volumes. The colors in the image represent the obtained t-values. L, left hemisphere; R, right hemisphere.

Discussion

The first aim of this research was to study the GM/WM volumes in male participants with AUD without FHA compared to HC. We expected to find that people with AUD will have lower GM/WM volumes in different brain regions than controls. This hypothesis has been partially confirmed since people with AUD have lower GM volumes in different brain regions than HC,

but this was not apparent for WM volumes. The regions with a reduced GM volume were the left superior temporal gyrus, bilateral parahippocampal gyrus, right uncus, bilateral insula, bilateral caudate, left putamen, bilateral amygdala, right anterior cingulate cortex, right thalamus, left claustrum, and left inferior frontal gyrus. These regions are involved in different functions that had been found altered in people who have developed an AUD with great importance in their prognoses, such as reward processing, behavioral learning and automatization, interoceptive integration, consideration of subjective values, reward expectations, and multi-cue associative learning (Koob and Volkow, 2010; Zilverstand et al., 2018). Since none of the participants had FHA, the obtained results reflect relatively purely the effects of chronic alcohol intake on brain volumes (De Bruin et al., 2005).

The results obtained in our study partially coincide with those obtained in different studies carried out to date, although not completely with any of them. Yang et al. (2016) also found reduced GM volume in the bilateral insula in their meta-analysis. Also like us, Grodin et al. (2013) found reduced GM volume in the right thalamus, and Chanraud et al. (2009) found reduced GM volume in the bilateral parahippocampal gyrus. In this line, Shim et al. (2019) also found reduced GM volume in the bilateral caudate, and Demirakca et al. (2011) also found reduced GM volume in the right anterior cingulum. However, although some of the other altered regions found in our study coincide with other authors' findings, the hemisphere does not. For example, van Holst et al. (2012) found a reduced GM volume in the right putamen, whereas we have found it in the left hemisphere. Yang et al. (2016) found reduced GM volume in the bilateral superior temporal gyrus in their meta-analysis, but we have found it in the left hemisphere. Demirakca et al. (2011) found a reduced GM volume in the right amygdala, whereas we have found it bilaterally. Grodin et al. (2013) found a reduced GM volume in the bilateral inferior frontal gyrus, but we have found it in the left hemisphere. Finally, Brooks et al. (2014) found a reduced GM volume in the left uncus, whereas we have found it in the right hemisphere.

In view of the results and the literature reviewed, although the study of GM volumes in people with AUD has been extensively developed, it is evident that the results are highly inconsistent between studies. The inconsistency is so high that even those meta-analyses that attempt to unify results provide different results among them (Xiao et al., 2015; Yang et al., 2016). As we suggest in the introduction section, the inconsistency may be due to the influence of different variables that are not always considered, such as the presence of FHA. Although the literature

has shown that the FHA has a differential effect on the brain tissues (Filippi et al., 2019; Gilman et al., 2007; Sjoerds et al., 2013), a large number of studies do not adequately control this variable. For example, we have not found any studies comparing people with AUD and HC in which the presence of FHA was an exclusion criterion. In fact, many of the studies we have reviewed do not even report this information from the sample of people with AUD, adding a possible interaction between chronic alcohol consumption and hereditary components associated with this disease. Therefore, this aspect may be an important cause of such inconsistency between neuroimaging studies that have been relatively minimized in this study.

Another way to understand why there is such a high inconsistency between studies is by looking for associations between different sociodemographic/clinical/self-assessment variables and brain tissues volumes. After our analyses, two significant inverse relationships have been found. Those variables that showed a significant relationship with the GM volume of different brain structures are the years of pathological alcohol consumption and the ADIS total score (that assesses the dependence intensity). Both variables would be two indices reflecting the chronicity, intensity, and severity of AUD. Thus, these relationships would suggest that the greater the chronicity/intensity/severity of AUD, the greater the extent of GM atrophy. Different studies have shown relationships consistent with those obtained in this work (Paul et al., 2008; Pfefferbaum et al., 1998; Thayer et al., 2016). Thayer et al. (2016) found significant negative associations between AUD severity and GM volume in the temporal, parietal, frontal, and occipital lobes, reflecting that the higher AUD severity, the smaller was the GM volume of these brain regions. Pfefferbaum et al. (1998) found that the amount of alcohol consumed by both people with AUD and HC during a 5-year follow-up could predict the rate of GM loss and sulcal expansion. Therefore, the fact that these variables appear to be related to GM volumes of different brain structures reflects the importance of taking these types of variables into account when performing a neuroimaging study.

In addition to the obtained results, some limitations of this work should be mentioned. The first and major limitation of this study is the sample size. The sample selection and the rigorous exclusion criteria used, such as the FHA, did not allow us to have a large final sample. However, this rigorous sample selection has allowed us to obtain much more accurate results about the effect of chronic alcohol consumption on brain volumes. Thus, it would be advisable to carry out similar studies with larger samples. The second limitation of the study is the resolution of the MRI used. Although a resolution of 1.5 T is acceptable for this type of study

with a clinical sample, with a higher resolution, it would be possible to obtain higher quality images and, therefore, more specific results.

In conclusion, the obtained results show that males with AUD without FHA have reduced GM volumes in several brain regions compared to HC without FHA. Likewise, we have also observed significant inverse associations of clinical/self-assessment variables about severity, intensity, and chronicity of AUD with GM volumes of regions distributed throughout the brain. GM structure integrity is relevant for the efficient functioning of low and high-order cognitive processes used in everyday life, and its damage has been seen related to the severity, intensity, and chronicity of the AUD. As such, it becomes relevant to assess and follow brain structural changes through the dependence course. In addition, because participants were carefully selected to reduce the potential confounding effects of hereditary components associated with the AUD, these results reflect relatively purely the effects of chronic alcohol intake on brain volume.

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