European Psychiatry 62 (2019) 107–115

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Family history of alcohol use disorder is associated with brain structural and functional changes in healthy first-degree relatives

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ARTICLE INFO

Article history:
Received 5 February 2019
Received in revised form 5 August 2019
Accepted 26 August 2019
Available online 24 September 2019

Keywords:
Alcohol use disorder
Childhood Trauma Questionnaire
Monetary Incentive Delay task
Relatives
Voxel-Based Morphometry
Vulnerability

ABSTRACT

Background: Neuroimaging studies of vulnerability to Alcohol Use Disorder (AUD) have identified structural and functional variations which might reflect inheritable features in alcohol-naïve relatives of AUD individuals (FH+) compared to controls having no such family history (FH-). However, prior research did not simultaneously account for childhood maltreatment, any clinically significant disorder and maternal AUD. Therefore, we mainly aimed to investigate the brain structure and reward-related neural activations (fMRI), using whole-brain analysis in FH+ young adults with no prevalent confounders.
Methods: 46 FH+ and 45 FH- male and female participants had no severe childhood maltreatment exposure, neither any psychiatric disorder or AUD, nor a prenatal exposure to maternal AUD. We used a 3 T MRI coupled with a whole brain voxel-based method to compare between groups the grey matter volumes and activations in response to big *versus* small wins during a Monetary Incentive Delay task. The Childhood Trauma Questionnaire score was used as confounding variable in the analyses to account for the remaining variance between groups.
Results: Compared to FH- controls, FH+ participants had smaller grey matter volumes in the frontal and cingulate regions as well as in the bilateral nucleus accumbens and right insula. The FH+ participants' fMRI datasets denoted a blunted activation in the middle cingulum with respect to FH- controls' during the processing of reward magnitude, and a greater activation in the anterior cingulum in response to anticipation of a small win.
Conclusions: Family history of alcohol use disorder is linked to structural and functional variations including brain regions involved in reward processes.

1. Introduction

Alcohol use disorder (AUD) is a leading cause of mortality, morbidity and disability worldwide [1]. AUD has been attributed to genetic predisposition for up to 40 to 60% [2,3], hence this risk in first-degree relatives of AUD individuals is much greater than in the general population [4]. Neuroimaging studies conducted among AUD individuals discussed inherent pre-existing variations entangled with the neurotoxic effects of alcohol use *per se* [5]. Hence, investigations in adolescents from AUD families provided evidence of structural [6–10] and functional [11–14] variations possibly reflecting vulnerability to AUD. In addition, there are prevalent confounders which may affect brain maturation such as childhood maltreatment, which is associated with psychopathology and risk of substance abuse [15,16]. Therefore, the previous

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http://dx.doi.org/10.1016/j.eurpsy.2019.08.003
0924-9338/

findings need to be re-evaluated to consider the prepotent influence of the maltreatment on structural deficits (*i.e.* smaller grey matter volumes) and functional overactivations in limbic regions that consistently include the hippocampus or the anterior cingulate cortex [17]. Maltreatment, even below the threshold of reportable childhood maltreatment, can lead to significant changes in the brain's emotion-regulating circuitry in adolescents [15]. In addition, chronic maltreatment is associated with cognitive deficits such as poorer inhibitory control [18] as described in adult first-degree relatives of AUD patients [19].

AUD adults indeed displayed grey matter volume (GMV) reductions in the hippocampus [20], amygdala [21], insula [22], caudate and putamen [23], cerebellum [24] as well as in the brainstem [25] compared to healthy controls using anatomical magnetic resonance imaging (MRI). GMV reductions were also observed in adolescents having a family history of AUD (called FH+) compared to those having no family history of AUD (called FH-) in the right amygdala [6], parahippocampal gyrus, thalamus, cingulum, superior frontal gyrus [7], orbitofrontal cortex [8] and cerebellum [9]. GMV reductions have also been reported in the parahippocampal gyrus [26] and in the amygdala [27] in FH+ healthy adults. Interestingly, GMV reductions observed FH+ individuals may indicate brain structural changes associated with a family history of AUD.

The most acknowledged mechanisms of vulnerability to addiction include functional deregulations of the reward system [28], intricately linked to deficits in inhibition [29] and sensation-seeking [30]. Functional magnetic resonance imaging (fMRI) showed that FH+ adolescents did not show variations of reward-related neural response [31,32] but had a blunted brain response to inhibition during Go/No-Go fMRI tasks [11,12,14]. However, short-term detoxified AUD individuals [33] and FH+ adults [34,35] had blunted activations in the ventral striatum during reward anticipation while performing a Monetary Incentive Delay (MID) task [36]. Elucidating whether reward processing in FH+ individuals is affected at the earliest stages has been deemed essential to better characterize the addictive behaviour' predisposition.

Although some previous studies controlled (as exclusion criteria or confounding variable in the analyses) for the confounding effects of any psychiatric disorder and AUD [11,13], maternal AUD [8,13,32], foetal alcohol syndrome [12,14,31] or even less frequently for maltreatment exposure [26], it is still unclear whether brain structural and functional features observed in FH+ individuals persist when controlling simultaneously for these confounding factors. Moreover, there have been calls for neuroimaging research on brain structure in healthy FH+ adults [19], since developmental maturation is still ongoing in adolescents [37]. In addition, previous studies on brain structure mostly predefined regions of interest, having possibly neglected some brain variations in FH+ individuals. Finally, although deficits in differentiating a big *versus* small reward were reported in other addictive disorders [38] and impairments in the computation of expected reward value have been identified in AUD individuals [39,40], it is unknown whether they might contribute to vulnerability to AUD.

To address these limitations, the primary aim of the study was to explore the whole brain structure and processing of reward magnitude in adult first-degree relatives of AUD individuals having no prevalent confounding factors (*i.e.*, severe maltreatment exposure, any clinically significant disorder, maternal AUD). The secondary aim was to assess inhibitory control to confirm inhibition deficits in a highly homogeneous sample. The Childhood Trauma Questionnaire (CTQ) score [41] was used as confounding variable in the statistical analyses. The tertiary aim was to explore on the whole brain the effects of low-to-moderate CTQ scores on brain structure and processing of reward in the FH+ group.

Firstly, based on prior research, we hypothesized smaller GMV in FH+ individuals in regions detailed above, *i.e.*, amygdala, parahippocampal gyrus, thalamus, cingulum, superior frontal gyrus, orbitofrontal cortex and cerebellum, and deficits in neural response to a big *versus* small win during a MID task. Secondly, we hypothesized poorer inhibition in cognitive tests in FH+ as compared to FH- participants. And thirdly, we hypothesized that exposure to low-to-moderate maltreatment can have a measurable impact on the brain *i.e.* structural deficits and reward-related overactivation in a group of FH+ individuals.

2. Material and methods

2.1. Participants' characteristics

Participants were recruited in the Department of Psychiatry and Addictology of the Corentin-Celton Hospital (Issy-les-Moulineaux, France). Participants from the FH+ group were mainly siblings of AUD patients followed in our department or participating in Alcoholics Anonymous, while participants from the FH- group were mainly psychology and medical students. The inclusion criteria were age ranging between 18 (age of civil majority) and 35, French native language, right-handed according to the Edinburgh Handedness Inventory scale. Healthy relatives of AUD individuals (FH+) were male and female defined as having two or more first or second-degree relatives with AUD including necessarily the father since inheritability to AUD has been found to be especially paternal [42] and excluding the mother to prevent foetal exposure to maternal AUD. Controls (FH-) were male and female defined as having no family history of AUD in neither first nor second-degree relatives.

Since we aimed to identify brain correlates of vulnerability to AUD rather than those of alcohol use *per se*, we considered the following exclusion criteria for the whole sample assessed using the Diagnostic Interview for Genetic Studies (DIGS [43,44]): past and current psychiatric diagnoses including abuse of or dependence to alcohol or other substances except tobacco according to DSM IV-TR criteria [45]. Current psychiatric diagnoses, including posttraumatic stress disorder, were also examined during a face-to-face interview with a psychiatrist. Using the DIGS, participants were also excluded if they fulfilled at least one of the following conditions: more than three alcohol intakes per week or more than six drinks per week for women or more than nine drinks per week for men, more than one episode of binge drinking (defined as drinking on the same occasion, *i.e.* at the same time or within a couple of hours of each other, five or more drinks for men and four or more drinks for women [46] over the past year and/or more than ten episodes in their lifetime; cannabis use in the last three months; use of prescribed and non-prescribed psychoactive drugs in the last six months; severe exposure to at least one form of childhood maltreatment, defined as having CTQ subscale scores $\geq$16, $\geq$13, $\geq$13, $\geq$18 and $\geq$13 for emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, respectively [47]. In addition to the excluded participants with maternal AUD, volunteers were not admitted to the study if they had a suspected foetal alcohol syndrome with generalized deficits in the processing and integration of information revealed by neurocognitive examination [48]. Exclusion criteria also involved other significant medical conditions such as medical events in perinatal history (perinatal foetal distress or prematurity of more than three weeks); any clinically significant or unstable disease; organic diseases affecting the central nervous system such as neurocognitive disorders, intellectual disabilities, history of head trauma with loss of consciousness and/or requiring hospitalization or meningoencephalitis; and MRI contra-indications.

https://doi.org/10.1016/j.eurpsy.2019.08.003 Published online by Cambridge University Press

The protocol of the study was approved by the Ile-De-France VIII ethics committee and by the National Agency of Security for French biomedical researches. All participants signed an informed consent after receiving full information on the study. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Data collection

2.2.1. Family history of AUD, clinical, sociodemographic and psychometric characteristics

Assessments have been performed face-to-face by the investigators. Family history of AUD was examined using the Family Informant Schedule and Criteria (FISC). Axis I psychiatric and substance use disorders were assessed with the DIGS during a face-to-face interview with a psychiatrist. Age, sex and education (in number of years of schooling) were also collected. Maltreatment exposure was assessed with the CTQ. Sensation seeking was assessed with the Sensation-Seeking Scale-Form V of Zuckerman [49]. Trait impulsivity was assessed with the Barratt Impulsivity Scale (11^{th} version) [50].

2.2.2. Magnetic resonance imaging (MRI)

Acquisitions of high-resolution images were conducted with a 3.0 T Siemens Trio scanner and a 12-channel coil at CENIR–ICM platform, Pitié-Salpêtrière Hospital (Paris, France). Pre-processing steps and statistical analyses were run with the Statistical Parametric Mapping software (SPM12, Welcome Trust Centre for Neuroimaging, University College London, UK).

2.2.2.1. Structural brain imaging. The anatomical 3D-T1-weighted sequence was carried out with the following parameters: sagittal slice plane, Repetition Time (TR) = 2.3 s, Echo Time (TE) = 2.93 ms, 256 × 256 view matrix, 160 slices, voxel size = 1.1 × 1.1 x 1.1 mm and duration = 554 s. A quality control has been conducted on T1 dataset from which images with a benign abnormality (n = 1), artifacts from excessive movements of the eyes's lens (n = 4) and head (n = 1) were excluded. The images were spatially normalized and segmented onto the MNI (Montreal Neurological Institute) tissue probability maps (TPM) into grey matter, white matter, cerebrospinal fluid, bone, soft tissue, background images – by fitting iteratively to TPM voxel's intensities [51]. Using the software R, the package "mvoutlier" detected extreme values from a normal distribution (https://cran.r-project.org/web/packages/mvoutlier/index.html) leading to the exclusion of outlier volumes (n = 4). Then, covariances were calculated with the tool "check sample homogeneity" (http://www.neuro.uni-jena.de/vbm/check-sample-homogeneity/) and volumes with covariances greater than two standard deviations from the mean were detected with the R package "extreme values" (https://cran.r-project.org/web/packages/extremevalues/index.html) thus outlier covariance volumes (n = 8) were excluded to control for errors of segmentation. Then, images were modulated and 10-mm full-width at half-maximum (FWHM) Gaussian kernel smoothed. Overall, following visual quality control and outliers' detection, 18 (19.8%) out of 91 acquisitions were excluded. The remaining sample for analysis was composed of N = 73 participants.

2.2.2.2. Functional brain imaging. An Echo-Planar Imaging sequence acquired 40 descending axial slices parallel to the anterior-posterior commissure for each n = 191 time-series, with the following parameters: thickness = 2.4millimeters (mm), TR = 2.2 s, TE = 30 ms, matrix size 64 × 64, voxel size = 3.4 × 3.4 x 2.4 mm and duration = 427 s. Excessive motion was prevented in the MRI with small wedges to fix head in place. Participants' blood oxygen level-dependent (BOLD) signal time course was recorded while performing an event-related revised MID task in which the main difference to the original version [52] is the omission of loss trials [53]. This task displayed sequences of clue, target and feedback phases. The clue indicated the amount of the gain and the participants were instructed to respond upon appearance of the target which occurred 4 s after the clue. Response was followed by a 1.5 s visual feedback informing the participants of their trial result (Supplementary Fig. A.1). There were 42 trials (14 no wins; 14 small wins; 14 big wins).

A visual quality control has also been conducted on functional data. Images were excluded in cases of truncation (n = 1), signal abnormality (n = 2), major artefact (n = 1) and sequence error (n = 1). No excessive motion was visually detected. Per participant, pre-processing steps included timing correction of the 40 slices per volume; rigid body realignment of the 191 volumes to the mean image; nonlinear normalization to MNI standardized space, intensity bias correction, writing of 3 mm^3 voxel-wrapped images which were finally 10-mm FWHM Gaussian filtered. Moreover, first-level analyses of BOLD signal changes were performed by adding anticipations and feedbacks as explanatory variables in the intra-subject model along with six motion realignment-computed parameters and derivatives. The canonical hemodynamic response function (HRF) accounted for lag between event onsets and effective BOLD signal changes. Participants not responding to all 'no win' conditions (n = 2) and with no or atypical BOLD signals in response to handgrip press were excluded (n = 6). Indeed, A quality control has been performed on fMRI "motor" contrasts (press left *minus* right, press right *minus* left) that usually displayed localized activations in the sensory / motor cortex and cerebellum. Therefore, any intense BOLD signal in the frontal, temporal or occipital lobe is atypical for motor contrasts (*e.g.* when the participant was not focusing on the task during the MID-task acquisition). Thus, out of the sample of 73 acquisitions, 13 (17.8%) were removed. Overall, the fMRI sample available for the second-level analyses was composed of N = 60 participants.

2.2.3. Cognitive assessments of inhibition

Participants performed the following cognitive tests: Go/No-Go test [54] and Hayling test [55]. Further details are given in the Supplementary Appendix A.1.

2.2.4. Statistical analyses

For all statistical analyses, age, sex and CTQ total score were included as confounding variables to account for residual variance between and within groups.

2.2.4.1. Voxel-Based Morphometry analyses. Voxel-Based Morphometry (VBM) analysis of grey matter images consisted of between-group voxel-to-voxel *t*-tests across the whole brain. The global GMV was added in the statistical model [56]. We used the xjView toolbox (http://www.alivelearn.net/xjview) to localise the regions of difference. Statistical maps had a height threshold at $p < 0.001$ uncorrected and an extent threshold at $p < 0.05$ Family-Wise Error (FWE) corrected (cluster size > 520 voxels). Because tobacco dependence [57] and cannabis use [58] may have confounding effects, we performed supplementary analyses with the number of pack-years of smoking or cannabis use as confounding variable.

We performed additional analyses to examine the confounding effects of the CTQ score on the GMV on the whole-brain within the FH+ group. Significance was set at a height threshold at $p < 0.05$ uncorrected and an extent threshold at $p < 0.05$ FWE corrected (cluster size > 8000 voxels).

https://doi.org/10.1016/j.eurpsy.2019.08.003 Published online by Cambridge University Press

2.2.4.2. Functional brain imaging analyses. Between-group comparisons of BOLD signal maps were also performed as voxel-to-voxel *t*-tests across the whole brain for the contrast of anticipation of a "big *versus* small win" [53,59] to assess neural response to the processing of reward magnitude; as well as for the two conditions independently, *i.e.* anticipation of a big win and anticipation of a small win. Statistical maps had a height threshold at $p < 0.001$ uncorrected and an extent threshold at $p < 0.05$ FWE corrected (cluster size > 80 voxels) [60]. The BrainVISA/Anatomist software (http://brainvisa.info) was used to build the figure which displays both structural and functional results. Because tobacco dependence [57] and cannabis use [58] might have confounding effects, we performed supplementary analyses with the number of pack-years of smoking or cannabis use as confounding variable.

The additional analyses to examine the confounding effects of the CTQ score on the BOLD signal within the FH+ group were significant at a height threshold at $p < 0.05$ uncorrected and an extent threshold at $p < 0.05$ FWE corrected (cluster size > 1250 voxels).

2.2.4.3. Sociodemographic, psychometric and cognitive analyses. Between-group differences regarding individual factors were tested using unequal variance *t*-tests or chi-square tests when the dependent variable was continuous or categorical, respectively. Between-group multivariable analyses were performed using linear or logistic regression when the dependent variable was continuous or binary, respectively. Statistical significance for cognitive data was determined using a two-sided alpha *a priori* set at 0.0036 (0.05 Bonferroni corrected *i.e.* divided by the number of tests, *i.e.* 14).

3. Results

3.1. Participants' characteristics

There were 73 participants included in the psychometric, structural and cognitive analyses; 37 participants with a family history of alcohol use disorder (FH+) and 36 controls having no such history (FH-). Participants' characteristics are given in Table 1. The total duration of education showed a non-clinically significant mean difference of 1.0 year. We found no significant between-group differences in age, sex, and substance use (all $p > 0.05$). However, we found a significantly greater severity of exposure to all childhood trauma subtypes in the FH+ participants compared to the FH- controls, except for sexual abuse which was not significantly different between groups.

3.2. Voxel-Based Morphometry analyses

Between-group comparison of grey matter images showed that the FH+ participants had significantly smaller GMV than the FH- controls in four clusters (Table 2; Fig. 1) comprising the right middle frontal gyrus, bilateral inferior frontal gyrus, right insula, bilateral nucleus accumbens, bilateral olfactory cortex, bilateral gyrus rectus, middle cingulate, bilateral precuneus and right pre- and post-central gyri. There was no region of larger GMV in the FH+ participants compared to the FH- controls. These results were conserved when adding the number of pack-years of smoking or cannabis use as confounding variable (Supplementary Fig. B.1; Supplementary Fig. D.1).

The confounding effects of the CTQ score in the FH+ group are shown in Supplementary Fig. C.1; Supplementary Table A.1. There were significant negative associations between the CTQ score and GMV volumes in the bilateral hippocampus, left para-hippocampal gyrus and bilateral cerebellum.

3.3. Functional brain imaging analyses

There were 60 participants included in the fMRI analyses (31 FH+ and 29 FH-). There was no significant between-group difference in their delayed final MID scores (means of 120.7 s (SD = 35.1) and 114.3 s (SD = 28.1) for FH+ and FH- participants, respectively; t=-0.12; $p = 0.90$). Between-group comparisons of neural response to a big *versus* small win indicated that the FH- controls had a significantly greater activation in the bilateral middle cingulum and right supplementary motor area (SMA) compared to the FH+ participants (Table 3; Fig. 1). As to the brain

Table 1
Comparisons of sociodemographic characteristics, childhood trauma exposure and substance use between participants with (FH+) and without (FH-) a family history of alcohol use disorder.

	FH+ participants [a] ($n = 37$)	FH- participants [a] ($n = 36$)	FH+ participants *vs* FH- participants	
Sociodemographic characteristics	**Mean (SD)**	**Mean (SD)**	**t** [μ]	***p* value**
Age	24.3 (4.2)	24.4 (3.7)	−0.16	0.870
Education (number of years of schooling)	13.9 (2.1)	14.9 (2.0)	−2.22	**0.030**
	%	**%**	x^2 [β]	***p* value**
Sex (male)	37.8	44.4	0.33	0.57
Childhood trauma exposure and substance use	**Mean (SD)**	**Mean (SD)**	**t** [μ]	***p* value**
CTQ total score (mean (SD), minimum, maximum)	46.6 (12.8), 27, 66	38.2 (7.0), 27, 53	3.46	**0.001**
Emotional abuse (mean (SD), minimum, maximum)	9.0 (4.9), 5, 15	6.8 (2.6), 5, 14	2.39	**0.019**
Emotional neglect (mean (SD), minimum, maximum)	13.9 (5.2), 5, 17	11.5 (3.9), 5, 17	2.25	**0.028**
Physical abuse (mean (SD), minimum, maximum)	6.4 (2.7), 5, 12	5.2 (0.6), 5, 8	2.57	**0.013**
Physical neglect (mean (SD), minimum, maximum)	8.8 (3.4), 5, 12	6.2 (1.9), 5, 12	3.93	<**0.001**
Sexual abuse (mean (SD), minimum, maximum)	8.5 (1.2), 6, 10	8.6 (1.1), 6, 10	−0.16	0.875
Number of standard alcoholic drinks per week	2.2 (3.0)	1.8 (1.8)	0.57	0.570
Number of pack-years of smoking	2.3 (3.4)	1.7 (3.0)	0.83	0.410
	%	**%**	x^2 [β]	***p* value**
Smokers	37.8	50.0	1.10	0.295
Lifetime cannabis use	73.0	66.7	0.35	0.557
Lifetime use of any other drugs	27.0	25.0	0.04	0.844

[a] Participants with a family history of alcohol use disorder had to have two or more first or second-degree relatives with alcohol use disorder (FH+) – including necessarily the father and excluding the mother. Controls had to have no family history of alcohol use disorder in neither first nor second degree relatives (FH-).
[μ] Unequal variance t-tests (df = 71).
[β] x^2 tests (df = 1). Continuous variables are presented as their mean values and standard deviation (SD). Categorical variables are presented as percentages. *p* values in bold are statistically significant ($p < 0.05$).

https://doi.org/10.1016/j.eurpsy.2019.08.003 Published online by Cambridge University Press

Table 2
Regions of reduction in grey matter volume in the participants having a family history of alcohol use disorder (FH+) compared to controls (FH-).

Region		Cluster level			Peak level	MNI Coordinates		
	BA	Cluster size (in voxels)	*p* value FWE corrected	*T*	*p* value uncorrected	x	y	z
Cluster 1								
R middle frontal gyrus	9	1368	**4.4072e-04**	5.97	**5.2166e-08**	28	40	34
R inferior frontal gyrus								
Orbital part	11			4.80	4.7218e-06	44	48	−9
Triangular part	45			3.89	1.1968e-04	46	44	0
Cluster 2								
R inferior frontal gyrus								
Opercular part	47	4599	**1.5614e-09**	5.79	**1.0702e-07**	48	10	2
Triangular part				4.36	2.2891e-05	56	22	14
L inferior frontal gyrus, Orbital part	11			4.23	3.6739e-05	−16	10	−20
R olfactory cortex	47			5.04	1.9367e-06	18	10	−18
L olfactory cortex	32			4.59	1.0342e-05	−6	20	−10
R insula				4.82	4.3244e-06	40	−4	8
L gyrus rectus	11			4.18	4.4344e-05	−6	33	−16
R gyrus rectus	11			4.15	4.8556e-05	4	44	−21
R nucleus accumbens				4.51	1.3629e-05	8	10	−10
L nucleus accumbens				4.17	4.4885e-05	−6	12	−8
Cluster 3								
Cingulum middle/posterior	31	1582	**1.5793e-04**	4.92	2.9949e-06	−2	−44	33
R precuneus	7			4.62	9.2786e-06	4	−54	21
L precuneus	31			4.21	3.8984e-05	−4	−57	32
R Calcarine fissure/lingual				3.69	2.2512e-04	10	−60	10
Cluster 4								
R precentral gyus	4	676	**0.0192**	4.47	1.5681e-05	44	−15	44
R middle frontal gyrus	6			4.17	4.5851e-05	39	−3	54
R postcentral gyrus				3.36	6.4635e-04	54	−8	36

BA: Brodmann Area (if region described by Brodmann); MNI: Montreal Neurological Institute (coordinates in mm); R: Right; L: Left; Extent threshold at $p < 0.05$ Family-Wise Error (FWE) corrected (cluster size > 520 voxels); Height threshold at $p < 0.001$ uncorrected. *p* values in bold are statistically significant ($p < 0.05$ FWE corrected). Sample size: n=37 FH+ and n=36 FH-.

activity in response to anticipation of a small win, the FH+ participants exhibited a significant greater activity than the FH- controls in the anterior cingulum (Table 3; Fig. 1). As to the brain activity in response to anticipation of a big win, no significant difference was observed between the groups. The same results were found when adding the number of pack-years of smoking or cannabis use as confounding variable (Supplementary Fig. B.2; Supplementary Fig. D.2).

The confounding effects of the CTQ total score in the FH+ group are shown in Supplementary Fig. C.2; Supplementary Table A.2. There were significant positive associations between the CTQ score and brain activation during the processing of reward magnitude in the bilateral parahippocampal gyrus, bilateral fusiform and lingual gyri, left cerebellum and right inferior frontal gyrus.

3.4. Cognitive measures

No significant between-group differences in the sensation-seeking and trait impulsivity scores were observed ($p < 0.001$) (Table 4). In the Hayling test, compared to the FH- controls, the FH+ participants showed significant increases in time response per sentence and corrected time response, and a significant lower number of accurate responses. In the Go/No-Go test, the FH+ participants made significantly more errors of commission and omission than the FH- controls ($p < 0.001$) (Table 4).

4. Discussion

This study sought to determine whether healthy adult first-degree relatives of individuals with AUD (FH+) differ from controls having no family history of AUD (FH-) in grey matter volumes (GMV), in brain response to a big *versus* small win during a Monetary Incentive Delay (MID) task, and in inhibition performance (Hayling and Go/No-Go tests). We ruled out the confounding effects of childhood maltreatment, and of any psychiatric disorder or AUD, and of prenatal exposure to maternal AUD. We found that family history of AUD was associated with i) smaller GMV in the frontal and cingulate regions as well as in the bilateral nucleus accumbens and right insula, ii) a blunted activation in the middle cingulum during the processing of reward magnitude and a greater activation in the anterior cingulum in response to anticipation of a small win, iii) and deficits in the accuracy of the inhibition processes and in the latency of the act of control. Overall, the present findings confirm and extend research on vulnerability to AUD.

On one hand, our findings are in line with previous studies on FH+ adolescents that showed localised GMV deficits compared to controls [6–9]. As previously identified in two distinct studies in FH+ adolescents [7,14], in the present study the middle cingulum was explicitly at the intersect of the brain structural (*i.e.* smaller GMV) and functional (*i.e.* blunted activation) differences between the FH+ and FH- participants. In healthy individuals, the volume of the middle cingulum underlies conflict monitoring [61] while its activity is typically involved during cognitive processing tasks [62].

On the other hand, we did not find smaller hippocampus in the FH+ participants when controlling for low-to-moderate exposure to childhood maltreatment as confounding variable (i.e variable of no interest in the statistical analyses), unlike previous studies conducted in FH+ adolescents [7], FH+ adults [26] and AUD individuals [20]. It remains unknown whether previous findings of hippocampal grey matter volume reductions were due to childhood trauma. However, childhood maltreatment exposure is known to impact the developing brain in numerous brain regions, the most consistently reported being the hippocampus as well as the anterior cingulate cortex [17]; and our additional findings

https://doi.org/10.1016/j.eurpsy.2019.08.003 Published online by Cambridge University Press

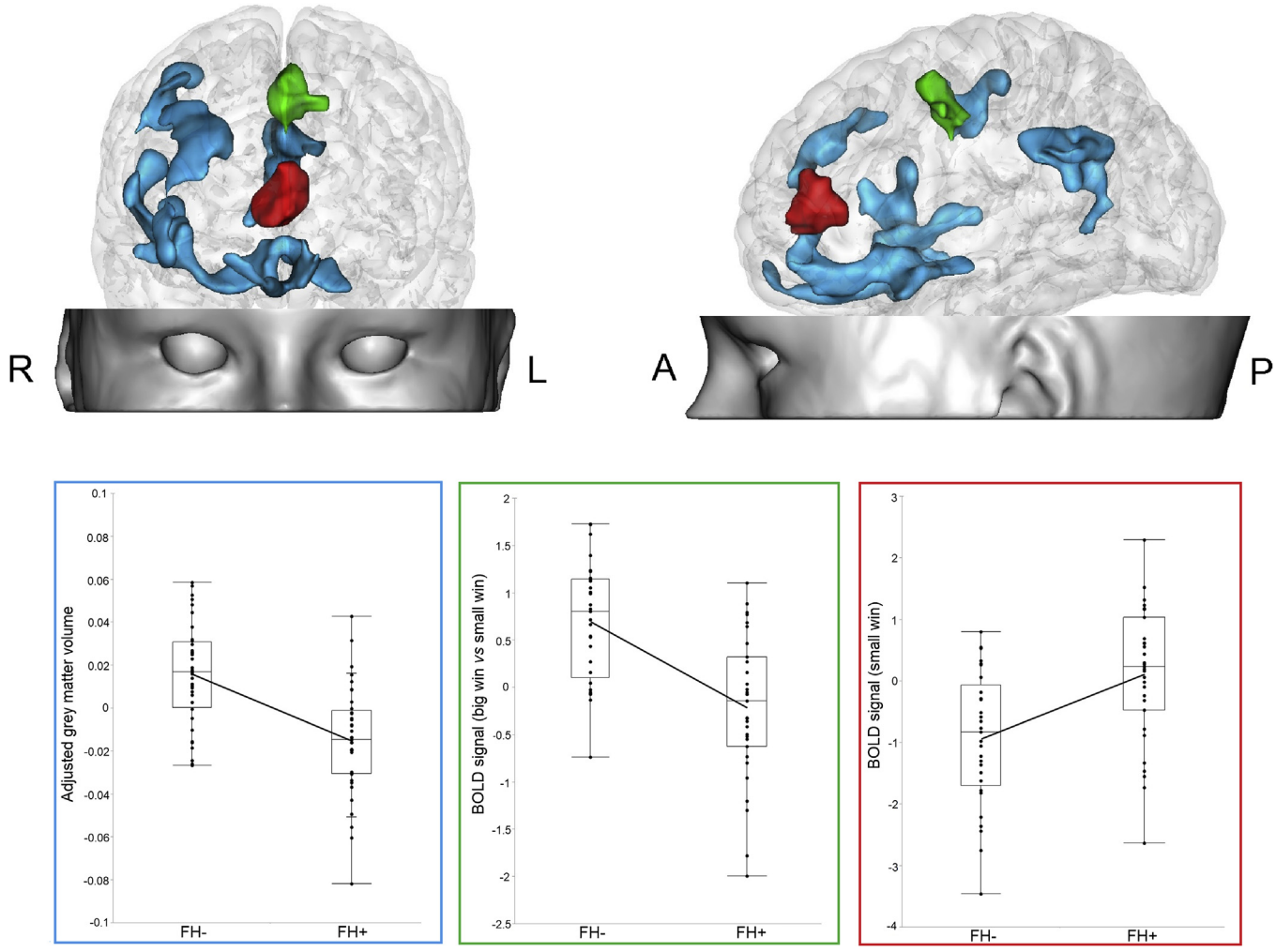

Fig. 1. Brain regions of differences in grey matter volumes and bold signal changes during anticipation of reward in a MID task between individuals with and without a family history of alcohol use disorder.
Participants with a positive family history of alcohol use disorder (FH+) presented smaller grey matter volumes in four clusters (blue colour) compared to participants having no family history of alcohol use disorder (FH-). FH+ individuals also had a blunted activation in response to a big *versus* small win (green colour) and a greater activation during anticipation of a small win (red colour) compared to FH- controls during the MID anticipation phase. Extent threshold was set at $p < 0.05$ Family-Wise Error (FWE) corrected; Height threshold was set at $p<0.001$ uncorrected. Each point on the boxplots represents the adjusted (for age, sex and Childhood Trauma Questionnaire total score) mean value for each participant. The line joining the boxplots spots the group mean. Orientation R: Right; L: Left; A: Anterior; P: Posterior; voxel resolution 1.5 × 1.5 x 1.5 mm; Montreal Neurological Institute space. Sample size: n = 37 FH+ and n = 36 FH- in the structural analyses; n = 31 FH+ and n = 29 FH- individuals in the functional analyses.

Table 3
Regions of BOLD signal changes in participants having a family history of alcohol use disorder (FH+) compared to controls (FH-) during a Monetary Incentive Delay (MID) task.

Region	BA	Cluster level		*T*	Peak Level	MNI Coordinates		
		Cluster Size (in voxels)	p value FWE corrected		p value uncorrected	x	y	z
Activation in FH- greater than in FH+								
Big win *versus* small win								
R supplementary motor area	6	89	**0.037**	4.55	1.5088e-05	6	−1	53
R middle cingulum				4.53	1.5867e-05	6	−7	47
L middle cingulum				3.56	3.8850e-04	−6	−4	44
Activation in FH+ greater than in FH-								
Anticipation of a small win								
Anterior cingulum		166	**0.008**	4.94	3.7777e-06	0	38	8
Anticipation of a big win								
Anterior cingulum		63	0.157	4.80	6.3054e-06	0	29	2

BA: Brodmann Area (if region described by Brodmann); MNI: Montreal Neurological Institute (coordinates in mm); R: Right; L: Left; Extent threshold at $p < 0.05$ Family-Wise Error (FWE) corrected (cluster size > 80 voxels); Height threshold at $p < 0.001$ uncorrected. *p* values in bold are statistically significant ($p < 0.05$ FWE corrected). Sample size: n=31 FH+ and n=29 FH-.

https://doi.org/10.1016/j.eurpsy.2019.08.003 Published online by Cambridge University Press

Table 4
Comparisons of personality and cognitive measures between participants with (FH+) and without (FH-) a family history of alcohol use disorder.

	FH+ participants [a] ($n = 37$)	FH- participants [a] ($n = 36$)	FH+ participants*vs* FH- participants	
	Mean (SD)	Mean (SD)	β (SE)[μ]	p value [μ]
Sensation Seeking Scale				
Total score	20.9 (5.7)	20.9 (6.7)	−0.83 (1.57)	0.599
Thrill seeking	6.2 (2.5)	6.7 (2.9)	−0.85 (0.68)	0.214
Inhibition	4.4 (2.4)	4.6 (2.6)	−0.36 (0.63)	0.568
Experience	6.6 (1.9)	6.3 (1.9)	0.21 (0.49)	0.678
Boredom Susceptibility	3.8 (2.1)	3.3 (2.0)	0.18 (0.52)	0.727
Barratt Impulsiveness Scale				
Total score	63.6 (10.4)	61.1 (7.0)	1.60 (2.22)	0.475
Attentional score	17.1 (3.4)	16.5 (3.0)	0.04 (0.81)	0.960
Motor score	22.2 (4.3)	17.1 (3.4)	0.52 (1.05)	0.620
Nonplanning score	24.3 (4.8)	23.3 (2.6)	1.03 (0.97)	0.292
Hayling Sentence Completion Test				
Time response per sentence (seconds)	7.9 (2.1)	5.8 (0.9)	1.92 (0.41)	<**0.001**
Corrected time response	88.9 (52.6)	32.1 (11.6)	55.49 (9.97)	<**0.001**
Penalties	9.2 (7.4)	5.8 (5.4)	4.60 (1.66)	0.007
Number of accurate responses	8.0 (3.9)	13.4 (6.3)	−5.92 (1.34)	<**0.001**
Go/No-Go Test				
Total number of errors of commission and omission	1.6 (1.4)	0.5 (0.7)	1.17 (0.30)	<**0.001**

[a] Participants with a family history of alcohol use disorder had two or more first or second-degree relatives with alcohol use disorder (FH+) – including necessarily the father and excluding the mother. Controls had no family history of alcohol use disorder in neither first nor second degree relatives (FH-). SD: standard deviation.
[μ] Unstandardized β coefficients and their standard errors (SE) were estimated through linear regression and adjusted for age, sex and Childhood Trauma Questionnaire total score (df = 4). p values in bold are statistically significant (alpha set *a priori* at 0.05/14 = 0.0036 Bonferroni corrected).

suggest that low-to-moderate maltreatment exposure may have an impact in FH+ participants on both brain structure and activity in the hippocampal and cerebellar regions.

Using the whole-brain method instead of the region-of-interest approach, additional brain regions were detected compared to earlier studies with FH+ individuals. We found that the FH + participants had smaller GMV in the bilateral nucleus accumbens, a core region of the reward system involved in the addictive processes. Prior research conducted among AUD individuals showed GMV reductions in the caudate nucleus and putamen compared to healthy controls [23], supporting the hypothesis that this variation might pre-exist in the vulnerable individuals. Similarly, the insula, part of the paralimbic region, was altered in the present sample of FH+ participants on the right side, as previously described in AUD individuals [22] and tobacco smokers [63,64].

Despite similar MID-task performance between groups regarding brain function, the FH+ participants had a blunted activation in the middle cingulum in response to the processing of reward magnitude. Deficits in the computation of expected values have been linked to impaired reward-based decision making [65] thus may contribute to vulnerability to AUD. However, the FH+ individuals showed an overactivity of the anterior cingulum compared to the FH- controls; a region that is thought to translate neural signals related to degree of reward expectancy [66] and is involved in the reward system [28]. Among detoxified AUD individuals, self-efficacy to abstain was positively associated with the neural response in the anterior cingulum during the MID anticipation phase [67], thus this overaction might denote a protective factor to AUD.

Deregulations of the inhibitory control have been largely reported in functional studies in FH+ adolescents [11,12,14]. We confirmed that the FH+ group had deficits compared to the FH- group in both cognitive tasks of inhibition, supporting the validity of the present sample. Deficient inhibitory control indicates poorer resistance to distractor or proactive interference [68], leading to a greater likelihood that a response will be executed rather than withheld [69]. Although inhibitory control has been identified as a main component of impulsivity [70], we did not find significant between-group differences neither for the Barratt Impulsivity Scale score nor for the Sensation-Seeking Scale score that are associated with substance misuse in young individuals [53]. Hence, the absence of such personality variations might denote a protective factor to AUD in the healthy FH+ individuals.

Despite the strengths of the study design involving participants with fewer confounding factors than previous studies, this design aiming to examine more specifically brain correlates of vulnerability to AUD, had some limitations. Firstly, there was no group of AUD individuals to compare with the FH+ participants. This would allow to disentangle the neural correlates of vulnerability to AUD from the mixed effects of alcohol intoxication observed in AUD individuals [5]. Secondly, although we excluded participants with severe exposure to any childhood maltreatment type, FH+ participants still had substantially higher CTQ scores than FH- participants. Thirdly, we excluded participants with AUD and maternal AUD exposure, however we cannot exclude potential brain and/or cognitive alterations due to past minimal alcohol use or minimal foetal alcohol exposure. Fourthly, psychiatric disorders were assessed following DSM-IV-TR criteria and not DSM-5 criteria. Fifthly, future studies with greater statistical power would benefit in examining whether our results hold or differ in women and men. Finally, we cannot exclude that observed differences may reflect protective factors in the FH- group instead of vulnerability factors in the FH+ group.

5. Conclusions

We showed that adult first-degree relatives of AUD individuals display GMV reductions in the frontal and cingulate regions, as well as a blunted activation in the middle cingulum in response to the processing of reward magnitude during a MID task. Moreover, our findings highlight pre-existing structural deficits in the nucleus accumbens and right insula, and an overactivation in the anterior cingulum in response to anticipation of small non-drug rewards. This study confirms and extents prior research on relatives of AUD individuals, and encourages to systematically control for the confounding effect of childhood maltreatment among other confounders, *i.e.* any clinically significant disorder and exposure to maternal AUD, in the study of vulnerability to AUD.

https://doi.org/10.1016/j.eurpsy.2019.08.003 Published online by Cambridge University Press

Declaration of Competing Interest

Frédéric Limosin has received speaker and consulting fees from Astra Zeneca, Euthérapie-Servier, Janssen, Lundbeck, Otsuka Pharmaceuticals and Roche. The present work is unrelated to these relationships. Other authors have no conflicts of interest or financial disclosures to make.

Acknowledgements

This research was supported by the French Ministery of Health (Programme Hospitalier de Recherche Clinique P110132, 2011), the Fondation pour la Recherche Médicale (DPA20140629802, 2014) and the Fédération pour la Recherche sur le Cerveau (C16/0932A01, 2016). The study was sponsored by Assistance Publique Hopitaux de Paris, represented by the HEGP Clinical Research Unit (Pr Gilles Chatellier). We would like to thank the team of CENIR – Centre for NeuroImaging Research, ICM - Institut du Cerveau et de la Moelle épinière, Hôpital Pitié-Salpêtrière, Paris, France. We would also like to thank the IMAGEN consortium that provided the revised version of the Monetary Incentive Delay task and Joelle Francis for her advices.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurpsy.2019.08.003.

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