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Brain structural magnetic resonance imaging predictors of brief intervention response in individuals with alcohol use disorder

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Abstract

Aims: Magnetic resonance imaging (MRI) studies have identified brain structural predictors of treatment response in individuals with alcohol use disorder (AUD) but with varying findings and primarily in male veterans. The present study investigated cortical surface area and thickness (CT) as predictors of brief intervention response in community-based adults with AUD.

Methods: Sixty-five non-treatment-seeking adults with AUD (44.6% male, aged 33.2 ± 1.3 years) underwent an MRI and received a brief intervention comprising personalized feedback and motivational interviewing, with follow-up ~6–8 weeks later to quantify changes in drinks/week (DPW), the primary outcome. Eighteen bilateral *a priori* regions of interest (ROIs) were used to predict DPW at follow-up, adjusting for baseline drinking. Significant predictors were examined with secondary outcomes, percent drinking and heavy drinking days, and in relation to out-of-scanner measures of impulsivity and comorbidities.

Results: Participants exhibited significant decreases in alcohol consumption in response to the brief intervention. Eight bilateral CT ROIs in the frontal, temporal, and occipital lobes, most notably medial orbitofrontal, middle temporal, and lateral occipital gyri, predicted DPW; however, only three predicted the secondary outcomes. Significant associations were observed between CT in frontal and occipital regions and impulsivity (delay discounting, lack of premeditation), executive functioning, anxiety, and stress.

Conclusions: Thinner frontal, temporal, and occipital ROIs predicted poorer brief intervention response, with notable overlap with brain regions previously implicated in AUD. Clarifying whether these regions reflect premorbid or acquired differences and, if the latter, the potential for recovery of cortical gray matter following drinking reductions are future priorities.

Keywords: alcohol use disorder; MRI; neural correlates; brief intervention; alcohol; neural biomarkers

Introduction

Globally, alcohol is the most widely used substance with roughly 7% of the population reporting consumption that is consistent with alcohol use disorder (AUD) (World Health Organization 2024). Based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), individuals meet the criteria for AUD upon fulfilment of at least 2 of 11 criteria, including items such as previous attempts or desire to reduce alcohol consumption; alcohol craving; social, health, or occupational consequences of use; tolerance; and withdrawal (MacKillop *et al*. 2022). Moreover, individuals with AUD often demonstrate higher levels of mood disorders, such as anxiety and depression, stress (Castillo-Carniglia *et al*. 2019), and impulsivity (Dick *et al*. 2010), as well as poorer neurocognitive and executive function (Maharjan *et al*. 2022). Due to its heterogeneous nature and compounded by these additional features, AUD remains difficult to understand and treat, with many individuals struggling to successfully reach abstinence (Creswell and Chung 2018).

There has been rising interest in leveraging neuroimaging, including magnetic resonance imaging (MRI), to better characterize the impact of chronic alcohol consumption on the brain. MRI studies of brain structure and function have identified neurobiological phenotypes of AUD (Arienzo *et al*. 2020; Dennis *et al*. 2020; Gerhardt *et al*. 2022). Compared to healthy controls, global reductions in cortical gray matter volume and thickness are consistently reported among AUD samples, as well as in regions such as the dorsolateral

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prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC) (Morris *et al.* 2019; Spindler *et al.* 2021; Daviet *et al.* 2022).

Several existing studies have found that cortical volume and thickness predict treatment response in AUD (Durazzo *et al.* 2011, 2017; Durazzo and Meyerhoff 2017, 2020). Previous studies have found that larger frontal (i.e., DLPFC), ACC, OFC, and insula volumes were associated with better clinical outcomes after 3–12 months (Moeller and Paulus 2018; Durazzo and Meyerhoff 2020); however, there is considerable variability in findings across studies. In addition, the existing research predominantly represents samples of male veterans with other comorbidities and does not evaluate nonabstinent treatment outcomes, which may conceal important neurobiological aspects of treatment response (Creswell and Chung 2018; Shmulewitz *et al.* 2021). Therefore, the extant literature necessitates further investigation of brain morphometry predictors of intervention outcomes in AUD, specifically among more community-based samples to enhance generalizability and understanding.

The primary goal of the present study was to identify structural brain predictors of response to a brief intervention comprising personalized feedback with motivational interviewing in AUD+ adults from the general community. We examined cortical surface area and thickness in 18 brain regions previously implicated in AUD across larger neuroanatomical regions such as the DLPFC, OFC, and ACC, as well as regions implicated in reward, such as the insula (Rando *et al.* 2011; Durazzo and Meyerhoff 2017; Morris *et al.* 2019). Given the non-treatment-seeking nature of the present study's sample, nonabstinent outcomes being acceptable within the intervention, and evidence that nonabstinent endpoints reflect clinically meaningful benefits (Creswell and Chung 2018; Shmulewitz *et al.* 2021), the primary outcome was the change in the quantity of alcohol consumption (i.e., measured as standard drinks per week) post-intervention. However, to comprehensively capture alcohol consumption patterns following the intervention, as secondary outcomes, we also examined the percentage of days alcohol was consumed (i.e., percent drinking days) and percent of days of heavy drinking days (i.e. $\geq$ 4/3 standard drinks on 1 day for males/females; MacKillop *et al.* 2022). We hypothesized that greater intervention response (i.e., reduction in alcohol consumption) would be predicted by greater cortical thickness and surface area at baseline (Durazzo *et al.* 2011, 2017; Rando *et al.* 2011; Creswell and Chung 2018), although, given the variability in previous findings, we did not make specific differential hypotheses among the *a priori* regions of interest (ROIs).

Materials and Methods

Participants

Non-treatment-seeking AUD+ adults aged 21–55 years were recruited from the general community in Hamilton, ON, Canada, from June 2019 to December 2022 as part of a larger case–control design study. Participants were required to meet the following inclusion criteria: (i) current AUD (i.e., $\geq$ 2 DSM-5 symptoms), as determined by a semi-structured clinical interview; and (ii) consistently high alcohol consumption over the past 3 months, based on National Institute on Alcohol Abuse and Alcoholism guidelines (i.e., $\geq$ 14/7 standard drinks per week for males/females). Participants were also required to be right-handed and fluent English speakers. Exclusion criteria included: (i) MRI research contraindications (e.g., pregnancy, metal implants, claustrophobia); (ii) current substance use disorder other than alcohol, cannabis, or tobacco; (iii) weekly or greater use of recreational substances other than alcohol, cannabis, or tobacco; (iv) history of severe mental health disorder (e.g., schizophrenia, bipolar disorder); and (v) significant history of brain injury (e.g., repeated concussion, traumatic brain injury, stroke) or other neurological disorder (e.g. multiple sclerosis, epilepsy). All participants provided written informed consent, and the study procedures were approved by the Hamilton Integrated Research Ethics Board (#4551).

A total of 68 AUD+ participants completed the baseline, MRI, and follow-up assessments. Three participants were excluded from the present analysis due to poor MRI realignment during preprocessing, resulting in a total of 65 participants in the final sample (Table 1).

Procedures

Interested individuals were assessed for eligibility through a telephone interview or online screen. All participants completed (i) an in-person screening session to confirm eligibility based on alcohol consumption (or a virtual equivalent during COVID-19 pandemic restrictions), (ii) a baseline session that included out-of-scanner and clinical assessments, and (iii) an MRI session that was immediately followed by the brief intervention. Participants were reassessed ~6–8 weeks later (47.72 ± 8.54 days between sessions, range = 35–74 days) to quantify any changes in alcohol consumption; however, the duration range between these sessions varied as a result of scheduling and the number of additional brief intervention sessions (i.e., additional sessions needed to be at least 1 week apart) the participant chose to access.

In terms of brief intervention content, immediately after the MRI, participants met with a trained study clinician (i.e., clinical psychology doctoral trainees [M.G., E.L., and S.K.S.], supervised by a licensed psychologist [E.M.]) for a session comprising structured personalized feedback about drinking delivered with motivational interviewing. Brief interventions using these components have been found to be effective in reducing drinking among non-treatment-seeking individuals (MacKillop *et al.* 2022). More details can be found in the Supplementary Materials; however, all participants received the brief intervention, following the same manualized procedure.

Assessments

Demographics, clinical characteristics, and additional alcohol use disorder–associated features

At the first visit, participants were asked to provide demographic information including their age, sex assigned at birth, gender, race, years of education, and household income. As a measure of AUD severity during the baseline visit, participants were administered the Diagnostic Assessment Research Tool, a structured, clinician-reported tool based on the DSM-5 AUD criteria (Schneider *et al.* 2022). To determine the presence of a current AUD, participants were asked to respond based on their typical behaviour over the past 3 months. The 28-day Timeline Followback was used to assess drinking outcomes; specifically, participants were asked to recall the quantity and volume of alcohol consumption over the previous 28 days (Sobell and Sobell 1992). Participants were asked to recall estimates of alcohol consumption in standard drinks, which were then used to quantify the number of drinks per week,

Table 1. Participant characteristics ($n = 65$)

Indicator	Mean (SD)	*T* (*P*-value) (baseline vs. follow-up)	Cohen's *d*
Age	33.18 (1.30)		
Sex [male; *n* (%)]	29 (44.62)		
Race [European White, *n* (%)]	53 (81.54)		
Years of education	14.83 (2.97)		
Income (median)	$75 000–90 000		
Smoker [n (%)][a]	26 (4.00)		
Cannabis use [*n* (%)]			
Regular cannabis use[b]	52 (8.00)		
Cannabis use disorder[c]	10 (15.39)		
Alcohol use			
Baseline AUD symptoms[c]	6.51 (2.46)		
AUD severity [n (%)]			
Mild (2–3 symptoms)	8 (12.31)		
Moderate (4–5 symptoms)	19 (29.23)		
Severe (6+ symptoms)	38 (58.46)		
Drinking outcomes			
Drinks per week			
Baseline	25.70 (15.75)	5.00 ($P < .001$)	0.61
Follow-up	16.99 (12.60)		
% Drinking days			
Baseline	62.42 (23.45)	4.04 ($P < .001$)	0.53
Follow-up	48.68 (26.90)		
% Heavy drinking days[d]			
Baseline	38.19 (24.08)	2.54 ($P = .014$)	0.29
Follow-up	30.99 (25.44)		

Notes: Based on [a]self-report and confirmed with FTND score > 1 [b]weekly or greater cannabis use [c]WHO-ASSIST and DART scores at baseline [d]biological sex (i.e. males ≥4 drinks on a single occasion; females ≥3 drinks on a single occasion).

percent of drinking days, and percent of heavy drinking days (MacKillop *et al*. 2022).

For supplemental analyses to inform the functional relevance of observed associations, participants were administered out-of-scanner assessments of impulsivity using the Urgency-Premeditation-Perseverance-Sensation-Seeking-Positive Urgency Scale (UPPS) (Cyders *et al*. 2014) and delayed reward discounting paradigms (Koffarnus *et al*. 2015), as well as internalizing disorders including depression (9-Item Patient Health Questionnaire; Kroenke *et al*. 2001), anxiety (7-Item Generalized Anxiety Disorder assessment; Spitzer *et al*. 2006), and perceived stress (10-Item Perceived Stress Scale; Cohen *et al*. 1983). Finally, neurocognitive performance was assessed using the National Institute of Health (NIH) Toolbox Cognition Battery (Akshoomoff *et al*. 2013).

MRI data acquisition

Participants were scanned with a 3-Tesla whole-body GE Discovery 750 MRI scanner (General Electric, Milwaukee, WI, USA). T1-weighted whole-brain volumes were acquired using a 4:43 min BRAVO sequence with the following parameters: repetition time = 8.2 ms, echo time = 3.2 ms, inversion time = 450 ms, 12° flip angle, field of view = 25.6 cm, matrix = 256 × 256, and 160 contiguous 1 mm sagittal slices, resulting in 1 mm isometric voxels. Resting-state and task-based imaging runs were acquired after the T1 acquisition as part of the entire study protocol, resulting in a total scanning time of 60 min.

Data analysis

Drinks per week at baseline and follow-up were square root–transformed to normalize the data distributions. The percentage of drinking and heavy drinking days, as well as other study variables, were normally distributed and did not require transformation.

To improve precision, T1-weighted structural MR images were skull stripped using the AFNI program @SSwarper (Reynolds *et al*. 2023), followed by cortical parcellation and subcortical segmentation using the standard *recon-all* pipeline in FreeSurfer v7.3 (https://surfer.nmr.mgh.harvard.edu/). Full details outlining this pipeline can be found elsewhere (https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all); however, the *-noskullstrip* flag was added and the skull stripped output from @SSwarper was implemented instead (Reynolds *et al*. 2023). Following this processing stream, surface area and thickness estimates of the left and right hemispheres of *a priori* ROIs were extracted for further analysis. All images were visually inspected by two trained raters (T.L.H., C.M.W.).

Based on previous literature, we identified a set of 18 bilateral *a priori* ROIs (Durazzo *et al*. 2011; Rando *et al*. 2011; Durazzo and Meyerhoff 2017; Creswell and Chung 2018; Morris *et al*. 2019). We were interested in the surface area and thickness of cortical regions that have previously been implicated in AUD or as predictors of treatment response in AUD patients. We examined surface area and thickness independently for greater specificity and because they may reveal distinct information relative to their combined metric of volume (Durazzo *et al*. 2011). The ROIs were located in the following larger anatomical regions, calculated by combining parcellations based on the Desikan atlas (see Supplementary Table 1 for corresponding Desikan atlas regions): the DLPFC, ACC, OFC, inferior frontal gyrus, temporal lobe, portions of the parieto-occipital junction, somatosensory cortex, primary motor cortex, and lateral sulcus.

Statistical analysis

Baseline and follow-up alcohol consumption assessments were contrasted using paired-sample *t*-tests to quantify changes in drinking behaviours. To confirm changes in drinking behaviours were consistent when including covariates used in subsequent analyses, linear mixed modelling was conducted with age, sex, and smoking and cannabis use status as binary variables (i.e., smoking indicated by $1 \geq$ on Fagerström Test for Nicotine Dependence; cannabis use indicated by weekly or greater use of cannabis; Gabrys and Porath 2019) included in the model.

To assess the predictive utility of each ROI, a series of multiple linear regressions were conducted with drinks per week at follow-up as the outcome variable; each bilateral ROI as the predictor; and controlling for age, sex, intracranial volume, smoking status (Durazzo *et al.* 2007), cannabis use status (Lorenzetti *et al.* 2019), and drinks per week at baseline. False discovery rate (FDR) corrections (Benjamini and Hochberg 1995) were used to minimize type I error inflation for each ROI. To further reduce the type I error rate, ROIs were averaged across the left and right hemispheres to create a bilateral estimate. Bilateral ROIs that survived FDR correction (i.e., $q < 0.05$) were retained for further investigation of laterality differences to determine if meaningful hemispheric differences were present following the same statistical procedure.

Secondary analyses were conducted to assess the utility of each ROI in predicting changes in the percent of drinking and heavy drinking days at follow-up. Multiple linear regressions were conducted wherein the percent of drinking or heavy drinking days was the outcome variable and the same covariates were included. To avoid excessive type I error rate inflation, only bilateral ROIs that survived FDR correction in our primary analyses were examined. Implicated bilateral ROIs in the secondary analyses were also corrected for multiple comparisons using FDR.

Further, correlation analyses were conducted to determine whether any of the significant brain–behaviour relationships identified from the primary regression analyses were related to additional AUD-associated features such as anxiety, stress, neurocognition, and impulsivity.

All statistical analyses were conducted in R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Brief intervention response

All demographic and clinical characteristics are outlined in further detail in Table 1. Linear mixed modelling analyses demonstrated consistent patterns of changes in drinking outcomes (Supplementary Table 2). As expected, there were significant decreases in alcohol consumption at the follow-up visit (Table 1, Fig. 1). The largest effect was observed in reductions in drinks per week, where participants consumed an average of nine drinks fewer per week. Participants also demonstrated a mean decrease of 4 fewer days of any alcohol consumption (overall 14% reduction in drinking days) and 2 fewer days of heavy alcohol consumption (overall 7% reduction in heavy drinking days) over the previous 28 days. In terms of the clinical significance of the changes, 53.8% ($n = 35$) of the study participants exhibited at least a one-level reduction in hazardous alcohol consumption using the World Health Organization guidelines. These guidelines have been validated as reflecting a clinically important reduction (Shmulewitz *et al.* 2021).

Brain structural predictors of reduction in drinks per week

For cortical thickness, eight bilateral ROIs across the DLPFC, OFC, ACC, temporal lobe, and parieto-occipital junction were significant predictors of drinks per week beyond FDR correction (Table 2, Fig. 2). All coefficients were negative, demonstrating a consistent inverse relationship between cortical thickness and number of drinks per week at follow-up. The insula was nominally significantly associated with changes in drinking but not beyond FDR correction. In follow-up analyses by hemisphere, the rostral ACC and precuneus were significantly implicated in the right hemisphere only, suggesting potential lateralization within these two regions (Supplementary Table 3).

For surface area, only the *pars opercularis* was a nominally significant predictor of change in drinks per week but did not survive FDR correction (Table 2). No follow-up hemispheric analyses were warranted.

Brain structural predictors of percent drinking days and heavy drinking days

The eight implicated bilateral ROIs from the primary analysis were investigated in secondary analyses of percent drinking days and heavy drinking days. Greater cortical thickness of the middle and superior temporal and lateral occipital gyri were significant predictors of decreased percent drinking days beyond FDR correction (Table 3). With respect to hemispheric analyses, there appeared to be little specificity between the left and right hemispheres among the implicated brain regions, mirroring primary outcomes (Supplementary Table 4).

Cortical thickness of only the middle temporal gyrus significantly predicted lower percent of heavy drinking days following FDR correction (Table 3). Consistent with percent drinking days, the significant predictors lacked specificity across hemispheres (Supplementary Table 5).

Relationships between brain morphometry and collateral alcohol use disorder features

The following features associated with AUD were significantly correlated with brain measures of cortical thickness: lack of premeditation (via the UPPS) and rostral ACC, delayed reward discounting of $100 and rostral middle frontal gyrus, anxiety and medial orbitofrontal gyrus, perceived stress and lateral occipital gyrus, working memory (NIH Toolbox List Sorting) and lateral occipital gyrus, and attention and inhibitory control (NIH Toolbox Flanker) and posterior cingulate cortex (see Supplementary Fig. 1). Except for the relationship between anxiety and the medial orbitofrontal gyrus, and between attention and inhibitory control and the posterior cingulate, all associations were negatively correlated, demonstrating that participants with greater cortical thickness in the rostral ACC, rostral middle frontal gyrus, and lateral occipital gyrus showed lower levels of lack of premeditation, delayed reward discounting, and working memory, respectively.

Discussion

Following a brief intervention, participants in the present study demonstrated statistically and clinically significant

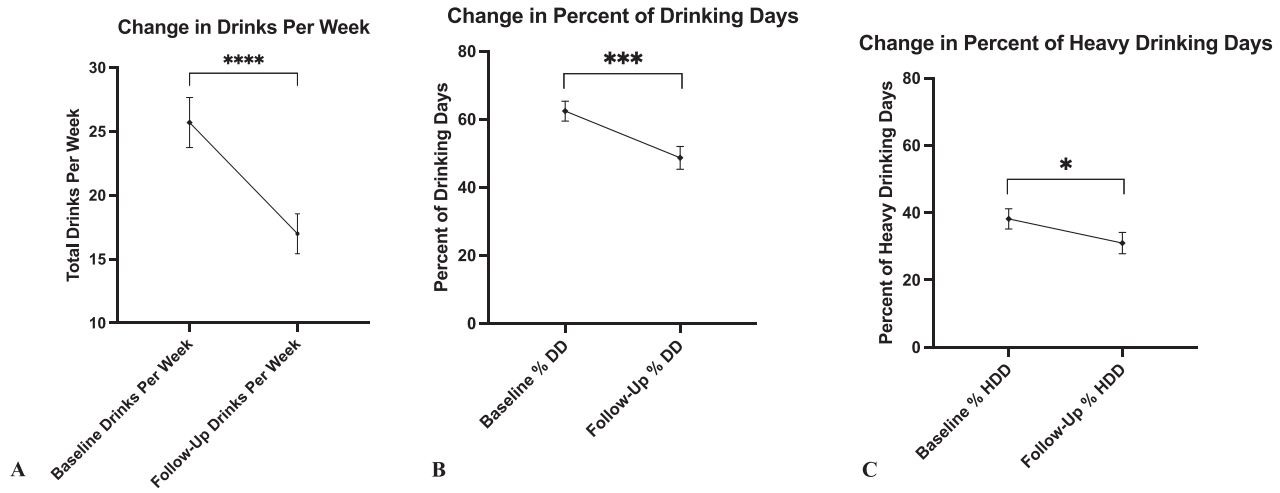

Figure 1 Line graphs demonstrating the changes in (a) drinks per week, (b) percent of drinking days, and (c), percent of heavy drinking days. Each diamond denotes the mean and standard error. ∗ $P < .05$, ∗∗ $P < .01$, ∗∗∗ $P < .005$, ∗∗∗∗ $P < .001$.

Table 2. Associations among bilateral *a priori* regions of interest and drinks per week at follow-up

Broader neuroanatomical region	Specific region of interest	Thickness		Surface area	
		B (95% CI)	*P*	*B* (95% CI)	*P*
Dorsolateral prefrontal cortex	Superior frontal gyrus	−0.35 (−0.646 to −0.044)	.025	0.23 (−0.087 to 0.553)	.150
	Caudal middle frontal gyrus	−0.13 (−0.414 to 0.147)	.345	0.21 (−0.061 to 0.478)	.128
	Rostral middle frontal gyrus	**−0.33 (−0.592 to 0.065)**	**.015**	0.17 (−0.167 to 0.401)	.412
Orbitofrontal cortex	Lateral orbitofrontal	−0.19 (−0.476 to .107)	.210	0.10 (−0.172 to 0.374)	.463
	Medial orbitofrontal	**−0.45 (−0.686 to −0.222)**	**< .001**	0.24 (−0.048 to 0.523)	.102
Anterior cingulate cortex	Caudal anterior cingulate	0.03 (−0.227 to 0.293)	.801	−0.10 (−0.361 to 0.167)	.463
	Rostral anterior cingulate	**−0.38 (−0.618 to −0.132)**	**.003**	0.09 (−0.162 to 0.342)	.478
Inferior frontal gyrus	Pars opercularis	−0.26 (−0.516 to −0.008)	.043	0.28 (0.017 to 0.534)	.037
	Pars orbitalis	−0.09 (−0.353 to 0.179)	.515	0.15 (−0.132 to 0.421)	.300
	Pars triangularis	−0.26 (−0.512 to −0.014)	.039	0.20 (−0.051 to 0.456)	.116
Temporal lobe	Middle temporal gyrus	**−0.54 (−0.762 to −0.310)**	**< .001**	0.21 (−0.080 to 0.505)	.150
	Superior temporal gyrus	**−0.36 (−0.594 to −0.127)**	**.003**	0.25 (−0.043 to 0.533)	.094
Parieto-occipital junction	Lateral occipital	**−0.36 (−0.577 to −0.140)**	**.002**	0.21 (−0.063 to 0.474)	.131
	Precuneus	**−0.32 (−0.563 to −0.069)**	**.013**	0.19 (−0.121 to 0.499)	.226
	Posterior cingulate	**−0.30 (−0.548 to −0.060)**	**.016**	−0.01 (−0.290 to 0.265)	.929
Primary motor cortex	Precentral gyrus	−0.21 (−0.473 to 0.058)	.124	0.21 (−0.068 to 0.490)	.135
Somatosensory cortex	Postcentral gyrus	−0.14 (−0.372 to 0.092)	.232	0.19 (−0.088 to 0.467)	.177
Lateral sulcus	Insula	−0.27 (−0.532 to −0.006)	.046	0.09 (−0.199 to 0.381)	.532

Notes: All multiple linear regressions were adjusted for age, sex, intracranial volume, smoking status (binary variable indicating weekly or greater recreational use of tobacco), cannabis use status (binary variable indicating weekly or greater recreational use of cannabis), and baseline drinks per week. Bolded values are retained after false discovery rate correction (i.e., $q < 0.05$).

reductions in drinks per week, percent of drinking days, and percent of heavy drinking days. Of the 18 *a priori* ROIs, thickness of the rostral middle frontal gyrus, medial OFC, rostral ACC, middle and superior temporal gyri, lateral occipital gyrus, precuneus, and posterior cingulate cortex were associated with reductions in standard drinks per week; participants who exhibited greater reductions in alcohol consumption, quantified by drinks per week, at follow-up showed greater cortical thickness at baseline. Our results are consistent with those of Durazzo *et al.*, who have repeatedly identified frontal brain region morphometry as predictors of treatment response in veterans with AUD. In their previous work, individuals who were unable to achieve remission demonstrated lower cortical surface area and thickness at baseline in the ACC, insula, OFC, regions in the DLPFC, and temporal gyri (Durazzo *et al.* 2011, 2017; Durazzo and Meyerhoff 2017, 2020; Durazzo *et al.* 2024).

Our results are also consistent with existing neurobiological structural and functional phenotypes of AUD. The DLPFC and ACC are frequently implicated in AUD-specific cognitive functions such as impulsivity, craving, decision-making, reward processing, goal-directed behaviours, and executive functioning (Dick *et al.* 2010; Castillo-Carniglia *et al.* 2019; Maharjan *et al.* 2022). Previous functional MRI studies have demonstrated aberrated blood-oxygen-level-dependent signalling and functional connectivity within and between the DLPFC, ACC, and OFC in AUD+ participants, as well as thinner cortices and smaller volumes of these regions, highlighting the neurobiological correlates between these regions and behaviours characteristic of AUD (Moorman 2018; Oberlin *et al.* 2020; Zeng *et al.* 2021; Murray *et al.* 2022; Atmaca *et al.* 2023; Kirsch *et al.* 2024). To explore whether these conclusions were supported in the present sample, we examined the relationships between these ROIs

Table 3. Associations between bilateral *a priori* regions of interest and percent drinking and percent heavy drinking days at follow-up

Broader neuroanatomical region	Specific region of interest	Percent of drinking days				Percent of heavy drinking days[a]			
		Thickness		Surface area		Thickness		Surface area	
		B (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*
Dorsolateral prefrontal cortex	Superior frontal gyrus	−0.33 (−0.635 to −0.030)	.032	0.29 (−0.025 to 0.605)	.070	−0.26 (−0.540 to 0.013)	.061	0.18 (−0.116 to 0.469)	.231
	Caudal middle frontal gyrus	−0.20 (−0.474 to 0.071)	.144	0.22 (−0.044 to 0.486)	.101	−0.18 (−0.433 to 0.077)	.167	0.11 (−0.142 to 0.355)	.395
	Rostral middle frontal gyrus	−0.33 (−0.588 to −0.065)[b]	.015	0.15 (−0.132 to 0.430)	.293	−0.24 (−0.486 to 0.001)[b]	.051	0.08 (−0.174 to 0.337)	.524
Orbitofrontal cortex	Lateral orbitofrontal	−0.11 (−0.405 to 0.179)	.443	0.10 (−0.169 to 0.372)	.456	−0.05 (−0.318 to 0.220)	.718	0.08 (−0.172 to 0.323)	.543
	Medial orbitofrontal	−0.29 (−0.536 to −0.039)[b]	.024	0.24 (−0.047 to 0.531)	.099	−0.29 (−0.511 to −0.063)[b]	.013	0.13 (−0.134 to 0.391)	.331
Anterior cingulate cortex	Caudal anterior cingulate	0.09 (−0.161 to 0.346)	.467	−0.09 (−0.348 to 0.178)	.520	0.11 (−0.117 to 0.345)	.327	−0.06 (−0.300 to 0.180)	.617
	Rostral anterior cingulate	−0.31 (−0.556 to −0.056)[b]	.017	0.12 (−0.137 to 0.374)	.356	−0.29 (−0.512 to −0.061)[b]	.014	0.10 (−0.133 to 0.323)	.408
Inferior frontal gyrus	Pars opercularis	−0.23 (−0.485 to 0.022)	.073	0.20 (−0.065 to 0.459)	.138	−0.21 (−0.437 to 0.026)	.081	0.19 (−0.053 to 0.429)	.124
	Pars orbitalis	−0.09 (−0.350 to 0.178)	.516	0.15 (−0.131 to 0.423)	.296	−0.09 (−0.340 to 0.153)	.450	0.13 (−0.123 to 0.379)	.312
	Pars triangularis	−0.26 (−0.506 to −0.014)	.039	0.14 (−0.112 to 0.400)	.264	−0.19 (−0.417 to 0.041)	.105	0.20 (−0.031 to 0.430)	.089
Temporal lobe	Middle temporal gyrus	**−0.52 (−0.753 to −0.290)**	**< .001**	0.24 (−0.052 to 0.522)	.106	**−0.50 (−0.705 to −0.303)**	**< .001**	0.10 (−0.165 to 0.373)	.440
	Superior temporal gyrus	**−0.38 (−0.614 to −0.149)**	**.002**	0.21 (−0.074 to 0.492)	.145	−0.28 (−0.496 to −0.064)[b]	.012	0.17 (−0.098 to 0.432)	.211
Parieto-occipital junction	Lateral occipital	**−0.33 (−0.551 to −0.108)**	**.004**	0.19 (−0.079 to 0.465)	.161	−0.25 (−0.457 to −0.051)[b]	.015	0.12 (−0.130 to 0.363)	.348
	Precuneus	−0.22 (−0.474 to 0.036)[b]	.091	0.19 (−0.114 to 0.489)	.217	−0.23 (−0.459 to 0.0002)[b]	.050	0.17 (−0.112 to 0.444)	.237
	Posterior cingulate	−0.26 (−0.503 to −0.014)[b]	.039	0.06 (−0.213 to 0.337)	.654	−0.22 (−0.449 to 0.001)[b]	.051	0.03 (−0.219 to 0.281)	.804
Primary motor cortex	Precentral gyrus	−0.24 (−0.502 to 0.018)	.068	0.20 (−0.073 to 0.480)	.145	−0.06 (−0.309 to 0.181)	.600	0.09 (−0.170 to 0.341)	.505
Somatosensory cortex	Postcentral gyrus	−0.19 (−0.417 to 0.040)	.104	0.28 (0.008 to 0.551)	.044	−0.09 (−0.304 to 0.118)	.382	0.14 (−0.111 to 0.394)	.266
Lateral sulcus	Insula	−0.24 (−0.505 to 0.029)	.079	0.05 (−0.237 to 0.341)	.719	−0.23 (−0.471 to 0.008)	.057	0.14 (−0.124 to 0.398)	.296

Notes: All multiple linear regressions were adjusted for age, sex, intracranial volume, smoking status (binary variable indicating weekly or greater recreational use of tobacco), cannabis use status (binary variable indicating weekly or greater recreational use of cannabis), and baseline percent of drinking days or percent of heavy drinking days. Bolded values are retained after false discovery rate correction (i.e. $q < 0.05$).
[a]Quantified based on sex (males ≥4 drinks on a single occasion; females ≥3 drinks on a single occasion). [b]Differs from the primary findings.

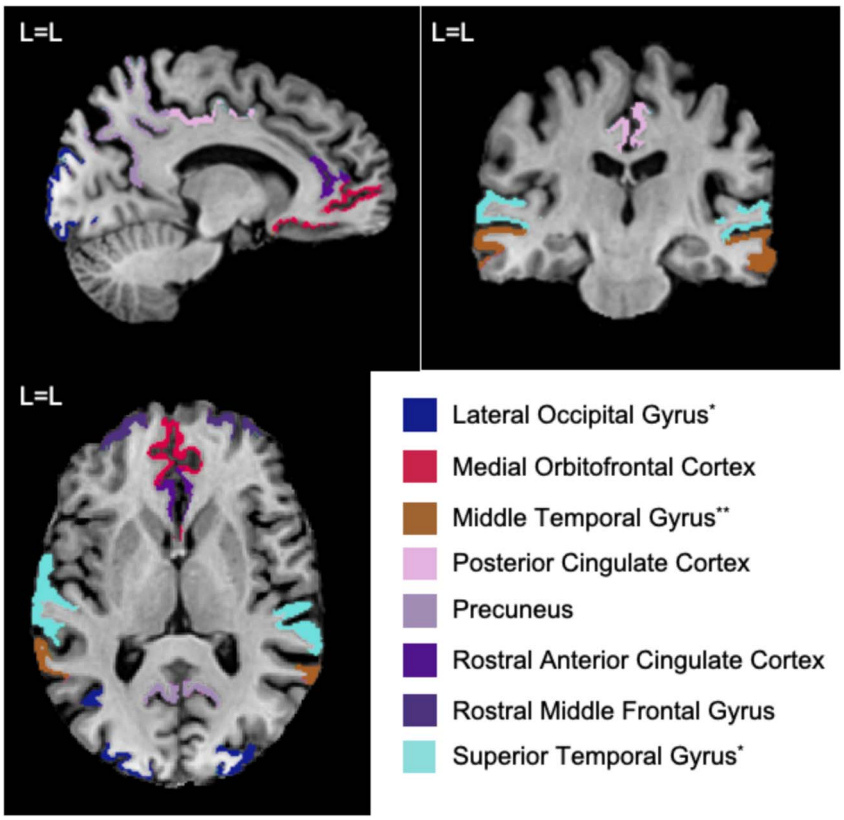

Figure 2 Significant bilateral *a priori* cortical thickness regions of interest in relation to changes in drinks per week at follow-up following the intervention. Regions that were implicated in secondary outcome analyses are indicated by * for percent of drinking days and ** for percent of drinking and heavy drinking days.

and key features of AUD. Impulsivity, executive function (i.e., working memory, attention, and inhibitory control), delayed reward discounting, and features of internalizing disorders were significantly correlated with the predictive ROI measures in the primary outcome assessments. Specifically, delayed reward discounting and lack of premeditation were negatively correlated with the rostral middle frontal gyrus and ACC, respectively, demonstrating that more impulsive individuals showed thinner cortical regions. Working memory, as measured by the list sorting task, and stress were negatively correlated with lateral occipital thickness. Anxiety and attention, and inhibitory control demonstrated a positive correlation, such that participants with higher levels of anxiety or attention/inhibition showed greater cortical thickness in the medial OFC and posterior cingulate, respectively; however, these findings were unexpected and necessitate further investigation. Taken together, these results demonstrate that in the present study, the individuals who were more impulsive, had higher levels of stress, and poorer cognitive function exhibited thinner DLPFC, ACC, and lateral occipital gyrus, as a group, which was also linked to a poorer response to the brief intervention.

We found that with drinks per week as the outcome, only the rostral ACC and precuneus were significant predictors in the right hemisphere; however, these analyses demonstrated overlapping 95% confidence intervals, suggesting there was no significant difference across hemispheres. While previous studies have found patterns of laterality in predicting alcohol initiation in adolescents and adults with AUD (Mashhoon *et al*. 2014; Rosenthal *et al*. 2019), there is an overall lack of literature discussing the impact of structural brain lateralization in AUD treatment. Therefore, additional research is necessary to better understand potential laterality as a predictor of change in drinks per week.

Thickness in the middle and superior temporal gyri and lateral occipital gyrus were also significant predictors of brief intervention response when assessing percent drinking days as the outcome; however, only the middle temporal gyrus was predictive of change in the percent of heavy drinking days. These results suggest that these regions are related to the frequency of drinking, not just the quantity. A potential explanation for this finding exists in the neurotoxic effect of alcohol; alcohol harms are dose-dependently related to the amount of alcohol consumption (MacKillop *et al*. 2022). The neurotoxicity of alcohol may affect brain regions differently; frontal brain regions appear to be more sensitive to the quantity of alcohol consumption since research demonstrates more prominent thinning in these regions (Nutt *et al*. 2021). However, further research is needed to identify any neuroprotective mechanisms in the DLPFC, precuneus, and posterior cingulate to higher frequency and intensity alcohol consumption.

Research has highlighted the distinct nature of cortical thickness and surface area, demonstrating the importance of assessing both measures in studies of brain morphology (Panizzon *et al*. 2009; Kremen *et al*. 2010; Winkler *et al*. 2010). While previous studies have found significant associations between AUD treatment outcomes and cortical surface area, none of the *a priori* ROIs in the current study were able to predict intervention response beyond FDR correction. The pars opercularis and postcentral gyrus were significant

predictors of response but were not retained following correction. These results, as well as the directionality and nominal significance of the other brain regions, are consistent with the existing literature demonstrating that greater cortical surface area can serve as a predictor of treatment response (Durazzo *et al*. 2011; Creswell and Chung 2018; Baranger *et al*. 2023); however, there is an overall lack of research aimed at understanding the relationship between cortical surface area and AUD interventions, warranting future investigation.

Future directions and limitations

The current study has a number of strengths. First, most similar studies consist of male veterans (Durazzo *et al*. 2011; Durazzo and Meyerhoff 2017, 2020; Durazzo *et al*. 2024), whereas the current study sample was recruited from the general community and the ratio of males and females is balanced. Additionally, previous research studies have dichotomized individuals into responder and nonresponder groups, which is defined as complete abstinence (Durazzo *et al*. 2011, 2017; Rando *et al*. 2011; Durazzo and Meyerhoff 2017, 2020). In the current study, we opted to assess treatment response in terms of alcohol consumption reduction, which may offer greater insights into brain structure underlying brief intervention response. Reciprocally, several limitations of the present study bear mentioning and can be used to inform future research. First, we assessed 18 ROIs that were selected based on previous research; future research may benefit from expanding to include additional ROIs that are implicated in other areas of cognition or substance use disorders. Next, while we did exclude participants with a significant history of brain trauma, neurological disorders, and MRI contraindications, we did not collect information from participants regarding all potential medical conditions that could be pertinent such as diabetes mellitus or hypertension. Future studies may benefit from collecting such information to confirm any relationships are not confounded by these factors. Moreover, while we included cannabis and smoking use as binary covariates, this approach did not allow for the assessment of potential dose-dependent effects or differences based on the route of administration, both of which may influence brain morphometry and brief intervention response; therefore, future studies may benefit from incorporating these factors into statistical analyses to better understand the relationship between substance use and clinical outcomes in AUD-focused interventions. Finally, it is unclear if the relationships observed in the current study are a direct result of chronic alcohol consumption (i.e., thinner cortical regions due to long-term drinking patterns) or if they reflect a potential neurobiological predisposition to the development of AUD. Previous studies have reported similar uncertainties regarding the directionality of such findings (Baranger *et al*. 2023); therefore, future longitudinal studies across the lifespan are necessary to better understand and characterize this relationship.

Conclusion

In the present study, we identified several brain regions with variations in cortical thickness that predicted response to a brief intervention in individuals with AUD. Participants with greater intervention response showed thicker cortical regions at baseline, representing potential neurobiological markers for treatment response. Regions that were predictive of outcome were primarily located in the frontal and temporal lobes, which are largely involved in cognitive processes including motivation and decision-making. These results may help to enhance understanding of the neural mechanisms underlying AUD intervention and response, thereby better informing treatment and intervention success.

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Author contributions

Tegan L. Hargreaves (Data curation, Methodology, Visualization [equal], Formal analysis [lead], Investigation [supporting]), Carly McIntyre-Wood (Data curation [equal], Formal analysis, Investigation, Methodology [supporting]), Emily Vandehei (Data curation, Investigation, Project administration [supporting]), Danielle Love (Data curation, Investigation [supporting]), Molly Garber (Data curation, Investigation [supporting]), Emily E. Levitt (Data curation, Investigation [supporting]), Sabrina Syan (Data curation, Investigation [supporting]), Emily MacKillop (Project administration [equal], Supervision [supporting]), Michael Amlung (Conceptualization, Formal analysis, Investigation, Methodology, Supervision [supporting]), Lawrence Sweet (Conceptualization, Funding acquisition, Methodology, Validation [equal], Data curation, Formal analysis, Investigation, Supervision [supporting]), and James MacKillop (Conceptualization, Funding acquisition, Methodology, Validation [equal], Data curation, Formal analysis [supporting], Investigation, Project administration, Supervision [lead])

Supplementary material

Supplementary data are available at *Alcohol and Alcoholism* online.

Conflict of interest: J.M. serves as a principal and senior scientist at BEAM Diagnostics, Inc. and has served as a consultant Clairvoyant Therapeutics, Inc. Neither had any role in the current research or any involvement in any aspect of this work.

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Data availability

Data are available upon request and approval of the PIs and relevant ethical review boards.

References

Akshoomoff N, Beaumont JL, Bauer PJ. *et al.* VIII. NIH toolbox cognition battery (CB): composite scores of crystallized, fluid, and overall cognition *Monogr Soc Res Child Dev*. 2013;**78**:119–32. https://doi.org/10.1111/mono.12038.

Arienzo D, Happer JP, Molnar SM. *et al.* Binge drinking is associated with altered resting state functional connectivity of reward-salience and top down control networks *Brain Imaging Behav*. 2020;**14**: 1731–46. https://doi.org/10.1007/s11682-019-00107-6.

Atmaca M, Tabara MF, Koc M. *et al.* Cortical thickness of the orbitofrontal cortex in patients with alcohol use disorder *Brain Sci*. 2023;**13**:552. https://doi.org/10.3390/brainsci13040552.

Baranger DAA, Paul SE, Hatoum AS. *et al.* Alcohol use and grey matter structure: disentangling predispositional and causal contributions in human studies *Addict Biol*. 2023;**28**:e13327. https://doi.org/10.1111/adb.13327.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing *J R Stat Soc Ser B Methodol*. 1995;**57**:289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x.

Castillo-Carniglia A, Keyes KM, Hasin DS. *et al.* Psychiatric comorbidities in alcohol use disorder *Lancet Psychiatry*. 2019;**6**:1068–80. https://doi.org/10.1016/S2215-0366(19)30222-6.

Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress *J Health Soc Behav*. 1983;**24**:385–96. https://doi.org/10.2307/2136404.

Creswell KG, Chung T. Treatment for alcohol use disorder: progress in predicting treatment outcome and validating nonabstinent end points *Alcohol Clin Exp Res*. 2018;**42**:1874–9. https://doi.org/10.1111/acer.13846.

Cyders MA, Littlefield AK, Coffey S. *et al.* Examination of a short English version of the UPPS-P impulsive behavior scale *Addict Behav*. 2014;**39**:1372–6. https://doi.org/10.1016/j.addbeh.2014.02.013.

Daviet R, Aydogan G, Jagannathan K. *et al.* Associations between alcohol consumption and gray and white matter volumes in the UK biobank *Nat Commun*. 2022;**13**:1175. https://doi.org/10.1038/s41467-022-28735-5.

Dennis LE, Kohno M, McCready HD. *et al.* Neural correlates of reward magnitude and delay during a probabilistic delay discounting task in alcohol use disorder *Psychopharmacology*. 2020;**237**:263–78. https://doi.org/10.1007/s00213-019-05364-3.

Dick DM, Smith G, Olausson P. *et al.* Understanding the construct of impulsivity and its relationship to alcohol use disorders *Addict Biol*. 2010;**15**:217–26. https://doi.org/10.1111/j.1369-1600.2009.00190.x.

Durazzo TC, Meyerhoff DJ. Psychiatric, demographic, and brain morphological predictors of relapse after treatment for an alcohol use disorder *Alcohol Clin Exp Res*. 2017;**41**:107–16. https://doi.org/10.1111/acer.13267.

Durazzo TC, Meyerhoff DJ. Changes of frontal cortical subregion volumes in alcohol dependent individuals during early abstinence: associations with treatment outcome *Brain Imaging Behav*. 2020;**14**:1588–99. https://doi.org/10.1007/s11682-019-00089-5.

Durazzo TC, Gazdzinski S, Meyerhoff DJ. The neurobiological and neurocognitive consequences of chronic cigarette smoking in alcohol use disorders *Alcohol Alcohol*. 2007;**42**:174–85. https://doi.org/10.1093/alcalc/agm020.

Durazzo TC, Tosun D, Buckley S. *et al.* Cortical thickness, surface area, and volume of the BRAIN reward system in alcohol dependence: relationships to relapse and extended abstinence: BRAIN REWARD SYSTEM IN RELAPSE AND ABSTINENCE *Alcohol Clin Exp Res*. 2011;**35**:1187–200. https://doi.org/10.1111/j.1530-0277.2011.01452.x.

Durazzo TC, Mon A, Gazdzinski S. *et al.* Regional brain volume changes in alcohol-dependent individuals during early abstinence: associations with relapse following treatment: brain volumes *Addict Biol*. 2017;**22**:1416–25. https://doi.org/10.1111/adb.12420.

Durazzo TC, Stephens LH, Meyerhoff DJ. Regional cortical thickness recovery with extended abstinence after treatment in those with alcohol use disorder *Alcohol*. 2024;**114**:51–60. https://doi.org/10.1016/j.alcohol.2023.08.011.

Gabrys R, Porath A. Clearing the smoke on cannabis: regular use and cognitive functioning. 2019. https://www.ccsa.ca/clearing-smoke-cannabis-regular-use-and-cognitive-functioning.

Gerhardt S, Karl D, Mann K. *et al.* Association between functional and structural brain connectivity of the default mode network in non-treatment seeking individuals with alcohol use disorder *Alcohol Alcohol*. 2022;**57**:540–51. https://doi.org/10.1093/alcalc/agab079.

Kirsch DE, Ray LA, Wassum KM. *et al.* Anterior cingulate and medial prefrontal cortex alcohol cue reactivity varies as a function of drink preference in alcohol use disorder *Drug Alcohol Depend*. 2024;**256**:111123. https://doi.org/10.1016/j.drugalcdep.2024.111123.

Koffarnus MN, Franck CT, Stein JS. *et al.* A modified exponential behavioral economic demand model to better describe consumption data *Exp Clin Psychopharmacol*. 2015;**23**:504–12. https://doi.org/10.1037/pha0000045.

Kremen WS, Prom-Wormley E, Panizzon MS. *et al.* Genetic and environmental influences on the size of specific brain regions in midlife: the VETSA MRI study *NeuroImage*. 2010;**49**:1213–23. https://doi.org/10.1016/j.neuroimage.2009.09.043.

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure *J Gen Intern Med*. 2001;**16**:606–13. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Lorenzetti V, Chye Y, Silva P. *et al.* Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies *Eur Arch Psychiatry Clin Neurosci*. 2019;**269**:59–71. https://doi.org/10.1007/s00406-019-00979-1.

MacKillop J, Agabio R, Feldstein-Ewing S. *et al.* Hazardous drinking and alcohol use disorders *Nat Rev Dis Primers*. 2022;**8**:80. https://doi.org/10.1038/s41572-022-00406-1.

Maharjan S, Amjad Z, Abaza A. *et al.* Executive dysfunction in patients with alcohol use disorder: a systematic review *Cureus*. 2022;**14**:e29207. https://doi.org/10.7759/cureus.29207.

Mashhoon Y, Czerkawski C, Crowley DJ. *et al.* Binge alcohol consumption in emerging adults: anterior cingulate cortical 'thinness' is associated with alcohol use patterns *Alcohol Clin Exp Res*. 2014;**38**:1955–64. https://doi.org/10.1111/acer.12475.

Moeller SJ, Paulus MP. Toward biomarkers of the addicted human brain: using neuroimaging to predict relapse and sustained abstinence in substance use disorder *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2018;**80**:143–54. https://doi.org/10.1016/j.pnpbp.2017.03.003.

Moorman DE. The role of the orbitofrontal cortex in alcohol use, abuse, and dependence *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2018;**87**:85–107. https://doi.org/10.1016/j.pnpbp.2018.01.010.

Morris VL, Owens MM, Syan SK. *et al.* Associations between drinking and cortical thickness in younger adult drinkers: findings from the human connectome project *Alcohol Clin Exp Res*. 2019;**43**:1918–27. https://doi.org/10.1111/acer.14147.

Murray L, Welsh JC, Johnson CG. *et al.* Alcohol- and non-alcohol-related interference: an fMRI study of treatment-seeking adults with alcohol use disorder *Drug Alcohol Depend*. 2022;**235**:109462. https://doi.org/10.1016/j.drugalcdep.2022.109462.

Nutt D, Hayes A, Fonville L. *et al.* Alcohol and the brain *Nutrients*. 2021;**13**:3938. https://doi.org/10.3390/nu13113938.

Oberlin BG, Shen YI, Kareken DA. Alcohol use disorder interventions targeting brain sites for both conditioned reward and delayed gratification *Neurotherapeutics*. 2020;**17**:70–86. https://doi.org/10.1007/s13311-019-00817-1.

Panizzon MS, Fennema-Notestine C, Eyler LT. *et al.* Distinct genetic influences on cortical surface area and cortical thickness *Cereb Cortex*. 2009;**19**:2728–35. https://doi.org/10.1093/cercor/bhp026.

Rando K, Hong K-I, Bhagwagar Z. *et al.* Association of Frontal and Posterior Cortical Gray Matter Volume with time to alcohol relapse: a prospective study *Am J Psychiatry*. 2011;**168**:183–92. https://doi.org/10.1176/appi.ajp.2010.10020233.

Reynolds RC, Taylor PA, Glen DR. Quality control practices in FMRI analysis: philosophy, methods and examples using AFNI *Front Neurosci*. 2023;**16**:1073800. https://doi.org/10.3389/fnins.2022.1073800.

Rosenthal A, Beck A, Zois E. *et al.* Volumetric prefrontal cortex alterations in patients with alcohol dependence and the involvement of self-control *Alcohol Clin Exp Res*. 2019;**43**:2514–24. https://doi.org/10.1111/acer.14211.

Schneider LH, Pawluk EJ, Milosevic I. *et al.* The diagnostic assessment research tool in action: a preliminary evaluation of a semistructured

diagnostic interview for DSM-5 disorders *Psychol Assess*. 2022;**34**:21–9. https://doi.org/10.1037/pas0001059.

Shmulewitz D, Aharonovich E, Witkiewitz K. *et al*. The World Health Organization risk drinking levels measure of alcohol consumption: prevalence and health correlates in nationally representative surveys of U.S. adults, 2001–2002 and 2012–2013 *Am J Psychiatry*. 2021;**178**:548–59. https://doi.org/10.1176/appi.ajp.2020.20050610.

Sobell LC, Sobell MB. Timeline follow-back. In: Litten RZ, Allen JP (eds.), *Measuring Alcohol Consumption*. Totowa, NJ: Humana Press, 1992, 41–72.

Spindler C, Trautmann S, Alexander N. *et al*. Meta-analysis of grey matter changes and their behavioral characterization in patients with alcohol use disorder *Sci Rep*. 2021;**11**:5238. https://doi.org/10.1038/s41598-021-84804-7.

Spitzer RL, Kroenke K, Williams JBW. *et al*. A brief measure for assessing generalized anxiety disorder: the GAD-7 *Arch Intern Med*. 2006;**166**:1092–7. https://doi.org/10.1001/archinte.166.10.1092.

Winkler AM, Kochunov P, Blangero J. *et al*. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies *NeuroImage*. 2010;**53**:1135–46. https://doi.org/10.1016/j.neuroimage.2009.12.028.

World Health Organization. *Global Status Report on Alcohol and Health and Treatment of Substance Use Disorders*. Geneva, 2024. https://iris.who.int/bitstream/handle/10665/377960/9789240096745-eng.pdf?sequence=1.

Zeng J, Yu S, Cao H. *et al*. Neurobiological correlates of cue-reactivity in alcohol-use disorders: a voxel-wise meta-analysis of fMRI studies *Neurosci Biobehav Rev*. 2021;**128**:294–310. https://doi.org/10.1016/j.neubiorev.2021.06.031.

Alcohol and Alcoholism, 2025, 60, agaf009
https://doi.org/10.1093/alcalc/agaf009
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