

Preserved Alcohol Cue Salience Despite Olfactory Dysfunction Is Associated with Multimodal Alterations in Olfactory–Reward Networks

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Abstract

Chronic alcohol consumption is associated with olfactory dysfunction, but the neurobiological mechanisms linking impaired olfactory function with alcohol cue responsiveness remain unclear. Ninety-eight alcohol consumers underwent objective olfactory assessment, a behavioral odor-cue task, structural MRI, fixel-based diffusion MRI, and proton magnetic resonance spectroscopy (MRS), and were classified as having normal olfactory function (threshold–discrimination score ≥ 16 ; $n = 54$) or olfactory dysfunction (score < 16 ; $n = 44$). Greater alcohol consumption was associated with poorer olfactory function ($r = -0.28$, $p < 0.01$). Despite olfactory dysfunction, familiarity with alcohol beverage odors was preserved, while alcohol cue-induced craving was greater at the highest alcohol concentration (42.8%; $\beta = 0.67$, $p = 0.04$). Compared to participants with normal olfactory function, those with olfactory dysfunction showed lower cognitive performance (Cohen's $d = -0.58$, $pFDR = 0.02$), smaller thalamic and amygdala volumes ($d = -0.70$ and -0.67 , $pFDR = 0.01$), reduced superior thalamic radiation fibre cross-section ($d = -1.30$, $pFDR < 0.001$), and lower prefrontal glutamate concentration ($d = -0.78$, $pFDR = 0.01$). The neurometabolite (MRS) composite was associated with alcohol consumption ($\beta = 0.52$, $p < 0.01$) and significantly mediated the association between olfactory dysfunction and alcohol consumption. Chronic alcohol consumption is thus associated with impaired olfactory function and coordinated neurometabolic, gray matter, and white matter alterations within an olfactory–reward network. Preserved familiarity and craving responses to alcohol-related odors despite impaired olfactory function suggest selective maintenance of alcohol cue salience and highlight olfactory dysfunction as a potential behavioral marker of alcohol-related brain dysfunction.

Introduction

Consumption of alcohol is a major contributor to global morbidity and mortality [1], with ethanol, the primary psychoactive and toxic constituent of alcoholic beverages, driving the development of alcohol dependence [2]. Chronic alcohol exposure induces widespread alterations in neural circuits involved in reward processing [3], motivated behaviour [4], and olfactory function [5–7]. Consequently, multiple aspects of olfactory function, including odor detection, discrimination, and identification [8, 9], are impaired with deficits becoming increasingly pronounced as alcohol use progresses to alcohol use disorder (AUD). These impairments extend beyond peripheral olfactory dysfunction and are accompanied by abnormalities within central olfactory pathways responsible for odor perception and cognitive processing [9, 10]. Despite increasing recognition of olfactory dysfunction in AUD, the neural mechanisms linking alcohol consumption to altered olfactory function remain poorly understood.

Accumulating evidence suggests that alcohol-related olfactory dysfunction may arise because olfactory perception and reward processing are supported by highly overlapping neural circuits [11–13]. Structural and functional neuroimaging studies have consistently demonstrated alcohol-related abnormalities in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula, amygdala, and medial temporal regions [14], all of which are involved in both odor processing and reward valuation. Likewise, structural MRI studies of olfactory dysfunction have reported reduced gray matter volume across primary and

secondary olfactory regions, including the piriform cortex, OFC, insula, cingulate cortex, and medial temporal structures [15]. Meta-analytic evidence further identifies the OFC as the cortical region most consistently associated with olfactory dysfunction, highlighting its role as a critical interface between sensory perception and reward-related decision-making [16]. Together, these findings suggest that alcohol consumption and olfactory dysfunction converge within a common olfactory–reward network.

Despite growing evidence that chronic alcohol exposure impairs odor detection, discrimination, and identification, alcohol-related odors remain potent triggers of craving and alcohol-seeking behaviour [17]. Alcohol-associated odor cues robustly activate mesocorticolimbic reward circuitry and reliably increase craving in individuals with AUD [11]. This apparent dissociation suggests that while general olfactory function deteriorates, the perceptual and motivational salience of alcohol-related odors may be preserved. Whether this reflects alterations within a shared olfactory–reward network remains unknown. Characterizing this dissociation requires examining how alcohol-related brain alterations relate to both general olfactory impairment and responsiveness to alcohol-associated odor cues. A multimodal approach may help determine whether these contrasting behavioral features are associated with a common pattern of neural alterations or with distinct neural substrates.

Beyond gray matter alterations, white matter connectivity and regional neurochemistry may provide complementary mechanisms linking alcohol use and olfactory dysfunction. Diffusion MRI studies have reported widespread abnormalities in fronto-limbic pathways in AUD, whereas recent voxel-based analyses demonstrate reduced fibre density and fibre cross-section in persistent olfactory dysfunction [18]. Similarly, proton magnetic resonance spectroscopy has revealed reduced N-acetylaspartate and altered glutamatergic metabolism in frontal regions [19, 20] involved in both olfactory processing and reward. However, these modalities have largely been investigated independently, and no study has examined whether multimodal structural and neurochemical alterations jointly explain alcohol-related olfactory dysfunction.

To our knowledge, no study has comprehensively examined objective olfactory function together with behavioral responses to alcohol-related odors, cortical morphology, white matter microstructure, and neurometabolite alterations within the same cohort. Determining whether these multimodal brain alterations represent a common olfactory–reward network may provide mechanistic insight into why alcohol-related odors retain their motivational salience despite impaired olfactory function.

We therefore investigated whether alcohol consumption severity is associated with (i) objective olfactory dysfunction and behavioral responses to alcohol-related odors, and (ii) multimodal neuroimaging measures encompassing cortical morphology, white matter microstructure, and neurometabolite concentrations. We further integrated multimodal imaging measures using principal component analysis and examined whether neurochemical alterations mediated the relationship between olfactory dysfunction and alcohol consumption. We hypothesized that increasing alcohol consumption would be associated with impaired olfactory function but preserved alcohol cue responsiveness, supported by multimodal alterations within a shared olfactory–reward network.

Methods

Participants

This study included 145 male participants aged 18–65 years who had consumed at least one alcoholic beverage within the preceding 12 months. Participants were recruited between August 2025 and July 2026 from the National Drug Dependence Treatment Centre (NDDTC), All India Institute of Medical Sciences (AIIMS), New Delhi, and from the local community through recruitment posters and word-of-mouth referrals. Female participants were not included because no eligible female inpatients with AUD were admitted to NDDTC during the recruitment period; only male participants were therefore included, to maintain demographic consistency across the study sample. Experienced psychiatrists (S.S. and Y.P.S.) at NDDTC diagnosed alcohol dependence ($n = 79$) according to the International Statistical Classification of Diseases and Related Health Problems, 11th Edition (ICD-11)[21]. Participants were enrolled as a part of an ongoing clinical trial (ICMR Trial No.: CTRI/2025/06/089858). The study protocol was approved by the Institutional Ethics Committees of the National Brain Research Centre (NBRC), Manesar, and AIIMS, New Delhi. Written informed consent was obtained from all participants prior to study participation.

Exclusion criteria included lifetime abstinence from alcohol, current use of hypoglycemic medications, a history of neurological disorders or traumatic brain injury, and active upper respiratory tract symptoms (e.g., common cold or influenza) that could affect olfactory function. All participants were scanned after being declared clinically stable by their treating clinicians, with neuroimaging performed 1–6 days following admission or treatment initiation. Behavioral assessments were conducted at both the National Drug Dependence Treatment Centre (NDDTC) and the National Brain Research Centre (NBRC), whereas all neuroimaging assessments were performed at NBRC. The study recruitment and assessment workflow is summarized in Fig. 1.

Clinical and Behavioral Assessment

All assessments were administered in both English and Hindi, as most participants were native Hindi speakers. Hindi translations of the assessment instruments were initially generated using Google Translate and subsequently reviewed and verified by two authors (T.B. and K.A.) were piloted in an independent cohort of 20 participants before implementation (all questionnaires are provided in Supplemental FileS1). A previously published Hindi version of MOCA was used [22].

Alcohol Consumption

Alcohol consumption was the primary explanatory variable and was quantified as a continuous measure. It was assessed on the day of clinical evaluation using two quantity–frequency items from the National Institute on Alcohol Abuse and Alcoholism Alcohol Consumption Scale: drinking frequency during the

preceding 12 months (item 4a) and the typical number of drinks consumed per drinking occasion (item 4b). A quantity–frequency (QF) index of weekly alcohol consumption was calculated by multiplying the values from these two items (4a and 4b) and dividing the product by 52 to estimate average weekly consumption[23]. To reduce positive skewness, the index was transformed as the natural logarithm of one plus the weekly consumption value. Because the highest response category of each item is open-ended and assigned a single numerical value, the QF index has a fixed upper limit of 245.7 drinks per week, producing a right censored distribution with 21 of 89 participants (24%) reaching this maximum. Censoring of an explanatory variable is not corrected by transformation and may introduce regression dilution, thereby attenuating estimated associations toward the null. We therefore additionally fitted a Tobit regression model [24], using a ratio of the Tobit model to ordinary least squares (OLS) slope to estimate the attenuation factor (Fig. 2A; Supplementary Methods in Supplemental FileS1).

Table 1

Demographic, clinical, and alcohol consumption characteristics by olfactory function (TD score < 16 = dysfunction, ≥ 16 = normal)

Variable	Olfactory dysfunction (n = 44)	Normal olfactory function (n = 54)	Statistic (df)	p	Effect size
Age (years)	38 (30.75–43)	34 (28.25–42)	H(1) = 2.27	.13	ε^2 = 0.02
Body mass index (kg/m ²)	22.7 (20.1–24.2)	23.1 (20.2–25.35)	H(1) = 0.17	.68	ε^2 = 0.002
Educational status			$\chi^2(4)$ = 2.17	.71	V = 0.15
No education	2 (5%)	4 (7%)			
Secondary school (till 10th grade)	15 (34%)	12 (22%)			
Senior secondary school (till 12th grade)	11 (25%)	13 (24%)			
Undergraduate (Bachelor's)	10 (23%)	15 (28%)			
Post-graduate (Master's) or higher	6 (14%)	10 (19%)			
Religious background			$\chi^2(7)$ = 7.98 (MC)	.29	V = 0.29
Buddhist	3 (7%)	0 (0%)			
Christian	1 (2%)	0 (0%)			
Hindu	36 (82%)	48 (89%)			
Jain	1 (2%)	0 (0%)			
Muslim	2 (5%)	3 (6%)			
Others	0 (0%)	1 (2%)			

Groups: Olfactory dysfunction (n = 44), Normal olfactory function (n = 54); total N = 98. Continuous variables: mean (SD) with one-way ANOVA (F, η^2) if normally distributed with homogeneous variance across groups (Shapiro-Wilk $p \geq .05$ in every group, Levene's $p \geq .05$); otherwise median (IQR) with Kruskal-Wallis (H, ε^2). Categorical variables: n (%) per category, each listed as its own row under the variable; χ^2 test, or Monte Carlo exact simulation (100,000 replicates) when > 20% of expected cell counts are below 5 (marked "MC"); Cramér's V. Standard drinks per occasion and age first started drinking: median (IQR), Kruskal-Wallis. Largest number of drinks in the last 12 months: originally a 10-level ordinal bin with irregular, partly overlapping ranges (1–2, 3–4, 5–7, 8–11, 12–23, 24+, 30+, 40+, 50+, More); ranked 1–10 by lower bound to compute a median category and Kruskal-Wallis. P values shown are raw (uncorrected). ^A Benjamini-Hochberg FDR-significant ($q < .05$), corrected once across all 21 variables in this table.

Variable	Olfactory dysfunction (n = 44)	Normal olfactory function (n = 54)	Statistic (df)	p	Effect size
Prefer not to say	0 (0%)	1 (2%)			
Sikh	1 (2%)	1 (2%)			
Family monthly income			$\chi^2(5) = 3.69$ (MC)	.61	V = 0.19
Below ₹25,000	5 (11%)	14 (26%)			
₹25,000 - ₹50,000	13 (30%)	12 (22%)			
₹50,000 - ₹1,00,000	10 (23%)	12 (22%)			
₹1,00,000 - ₹2,00,000	5 (11%)	5 (9%)			
Above ₹2,00,000	7 (16%)	6 (11%)			
Don't know / Prefer not to say	4 (9%)	5 (9%)			
Montreal Cognitive Assessment score (MoCA)	19 (16–23)	22 (20–25)	H(1) = 7.97	. < 0.01	$\epsilon^2 = 0.09$
Current smoking status	29 (66%)	25 (47%)	$\chi^2(1) = 2.70$	.10	V = 0.17
Fagerström test for nicotine dependence (FTND) score	6 (07)	3 (0–6)	H(1) = 4.10	.04	$\epsilon^2 = 0.05$
Psychiatric/psychological medication	13 (30%)	7 (13%)	$\chi^2(1) = 2.99$	.08	V = 0.18
Illicit drug use (marijuana)	9 (21%)	18 (34%)	$\chi^2(1) = 1.40$	.24	V = 0.12
Penn Alcohol Craving Scale (PACS) score	16.76 (7.19)	11.61 (7.47)	F(1,89) = 11.12	.01 ^A	$\eta^2 = 0.11$
Generalized Anxiety Disorder 7 (GAD-7) score	16.16 (4.393)	16.40 (4.07)	F(1,94) = 0.08	.78	$\eta^2 = 0.001$
Groups: Olfactory dysfunction (n = 44), Normal olfactory function (n = 54); total N = 98. Continuous variables: mean (SD) with one-way ANOVA (F, η^2) if normally distributed with homogeneous variance across groups (Shapiro-Wilk $p \geq .05$ in every group, Levene's $p \geq .05$); otherwise median (IQR) with Kruskal-Wallis (H, ϵ^2). Categorical variables: n (%) per category, each listed as its own row under the variable; χ^2 test, or Monte Carlo exact simulation (100,000 replicates) when > 20% of expected cell counts are below 5 (marked "MC"); Cramér's V. Standard drinks per occasion and age first started drinking: median (IQR), Kruskal-Wallis. Largest number of drinks in the last 12 months: originally a 10-level ordinal bin with irregular, partly overlapping ranges (1–2, 3–4, 5–7, 8–11, 12–23, 24+, 30+, 40+, 50+, More); ranked 1–10 by lower bound to compute a median category and Kruskal-Wallis. P values shown are raw (uncorrected). ^A Benjamini-Hochberg FDR-significant ($q < .05$), corrected once across all 21 variables in this table.					

Variable	Olfactory dysfunction (n = 44)	Normal olfactory function (n = 54)	Statistic (df)	p	Effect size
Patient Health Questionnaire-9	15 (12–17)	13.500 (10–17)	H(1) = 1.37	.24	ε^2 = 0.01
Perceived Stress Scale	18.74 (6.50)	19 (4.36)	F(1,91) = 0.05	.82	η^2 = 0.001
Threshold	6.40 (2.33)	11.35 (2.53)	F(1,96) = 99.53	< .01 ^A	η^2 = 0.51
Discrimination	6 (4–7)	10. (6.–12.75)	H(1) = 26.04	< .01 ^A	ε^2 = 0.27
Standard drinks per drinking occasion (median)	17.50 (6–35)	9.500 (3.50–35)	H(1) = 3.224	.073	ε^2 = 0.04
Average sessions in the last 12 months	300 (52–365)	30.000 (4..50–300)	H(1) = 11.912	< .001 ^A	ε^2 = 0.13
Largest number of drinks in the last 12 months (median)	24 + drinks (8–11 drinks–50 + drinks)	8–11 drinks (3–4 drinks–24 + drinks)	H(1) = 6.45	.011 ^A	ε^2 = 0.08
Age first started drinking	19. (18.–20.)	19. (18.–20.)	H(1) = 0.00	1.000	ε^2 = 0.000
Favourite alcoholic beverage			$\chi^2(3)$ = 4.01	.260	V = 0.24
Beer	9 (24%)	7 (19%)			
Coolers	3 (8%)	8 (22%)			
Liquor	14 (38%)	15 (42%)			
Wine	11 (30%)	6 (17%)			
Groups: Olfactory dysfunction (n = 44), Normal olfactory function (n = 54); total N = 98. Continuous variables: mean (SD) with one-way ANOVA (F, η^2) if normally distributed with homogeneous variance across groups (Shapiro-Wilk $p \geq .05$ in every group, Levene's $p \geq .05$); otherwise median (IQR) with Kruskal-Wallis (H, ε^2). Categorical variables: n (%) per category, each listed as its own row under the variable; χ^2 test, or Monte Carlo exact simulation (100,000 replicates) when > 20% of expected cell counts are below 5 (marked "MC"); Cramér's V. Standard drinks per occasion and age first started drinking: median (IQR), Kruskal-Wallis. Largest number of drinks in the last 12 months: originally a 10-level ordinal bin with irregular, partly overlapping ranges (1–2, 3–4, 5–7, 8–11, 12–23, 24+, 30+, 40+, 50+, More); ranked 1–10 by lower bound to compute a median category and Kruskal-Wallis. P values shown are raw (uncorrected). ^A Benjamini-Hochberg FDR-significant ($q < .05$), corrected once across all 21 variables in this table.					

Because the QF index contains no variability among participants assigned the maximum value, we additionally derived exposure measures that better reflected long-term alcohol use. Duration of drinking

(years) was calculated as the difference between current age and age at first alcoholic drink. Cumulative lifetime alcohol exposure was estimated as the product of the weekly QF index and drinking duration, expressed as drink-years and log-transformed before analysis. Drinking duration was also analysed independently to distinguish the effects of chronicity from those of cumulative alcohol dose. Because drinking duration is inherently correlated with age, all analyses involving duration or drink-years were additionally adjusted for age.

Olfactory Assessment

Olfactory function was assessed using the Sniffin' Sticks test battery [25], which evaluates odor threshold (T; using a three-alternative forced-choice (3-AFC) task [26]), discrimination (D), and identification (I). Because pilot testing in our study population indicated lower identification accuracy for several test odorants such as liquorice, cinnamon, lemon, turpentine and leather (Supplemental FileS1), we used a sum of odor threshold (exclusively uses phenyl ethyl alcohol, PEA or, rose odor that demonstrated high familiarity ratings) and discrimination score as the primary objective measure of olfactory function. The median TD score was the cut-off (TD = 16) for differentiating olfactory dysfunction (TD < 16) and normal olfactory function (TD ≥ 16).

Behavioral Odor-Cue and Craving Odor-Cue Task

Participants completed an odor-cue paradigm designed to assess perceptual, hedonic, familiarity, identification, and craving responses to alcohol-related and non-alcohol odors. The task included eight odor types representing five functional categories: (i) simulated alcoholic-beverage odors; (ii) ethanol; (iii) trigeminal odors: clove, cinnamon, and mint; (iv) appetitive odors: banana and vanilla; and (v) a neutral odor: rose. The alcoholic-beverage odors represented culturally familiar alcoholic beverages across commonly available alcohol strengths: beer, wine, country liquor, and whiskey.

All odor stimuli were custom-formulated and prepared for the present study by Ambrosia Botanicals (India). The simulated alcoholic-beverage odors were laboratory-prepared mixtures of ethanol and beverage-specific fragrances. The ethanol-only comparison stimuli were prepared from 99.9% pure laboratory-grade ethanol at corresponding concentrations of 8%, 13%, 25%, 37%, and 42.8% v/v. All the odorants were diluted in dipropylene glycol (DPG). More details of odorant preparation are provided in Supplementary Methods (Supplemental File S1).

Odor presentation and perceptual assessment: Odorants were contained in uniform roll-on vials and presented approximately 2 cm below the nostrils for 5 seconds. Participants sniffed each odor binarily. Participants were blind to the identity of the odors and no practice trial was administered. The task comprised five concentration blocks: 8%, 13%, 25%, 37%, and 42.8%, administered in ascending order. Each block contained eight odor trials presented in the following fixed sequence: alcoholic-beverage odor, clove, cinnamon, mint, banana, vanilla, rose, and ethanol. Each participant therefore completed 40

trials (with inter-trial stimulus interval of 30 seconds) across the five blocks. Immediately after each presentation, participants rated perceived odor intensity on a 0–10 visual analog scale (VAS) and pleasantness on a 0-100 VAS. Participants then indicated whether the odor was familiar using a yes/no response and attempted to identify it through open-ended naming.

Craving Odor-Cue task

Following completion of the perceptual assessment, the simulated alcoholic-beverage and ethanol odors were presented again, in paired ascending concentration order (each simulated beverage odor followed by corresponding ethanol-only odor) to assess alcohol craving following exposure to alcohol-related odors. Each odor was presented using the same procedure described above. After each presentation, participants rated their agreement, from 0 (complete disagreement) to 9 (complete agreement) with four statements adapted from items 11, 18, 22, and 32 of the Alcohol Craving Questionnaire–Now (ACQ-NOW)[27] (Supplementary Methods in Supplemental FileS1).

Cognitive and Clinical Measures

Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA)[28]. Current smoking status was obtained by self-report, and nicotine dependence among current smokers was assessed using the Fagerström Test for Nicotine Dependence (FTND)[29]. Symptoms of anxiety and depression were measured using the Generalized Anxiety Disorder-7 (GAD-7)[30] and the Patient Health Questionnaire-9 (PHQ-9)[31], respectively.

MRI Acquisition and Processing

All MR data were acquired at the National Neuroimaging Facility, NBRC, using a 3T Siemens MAGNETOM Prisma scanner (Siemens Healthineers, Germany) with a 64-channel head–neck coil. High-resolution three-dimensional T1-weighted (MPRAGE) images were quality-assessed with MRIQC [32] and processed using FreeSurfer (v8.2.0) to derive cortical thickness based on the Desikan–Killiany atlas [33]. Subject-specific piriform cortex masks were generated using multi-atlas propagation with enhanced registration (MAPER) [34, 35]. The anterior olfactory nucleus (AON) and olfactory tubercle (OT) gray masks were derived from the Sense of Smell atlas [36] and transformed into native space using ANTs-based nonlinear registration [37]. Whole-brain multi-shell diffusion-weighted images ($b = 500, 1000, \text{ and } 2000 \text{ s/mm}^2$) were pre-processed in MRtrix3[38] to derive diffusion tensor metrics and fixel-based measures - fiber density (FD), fiber bundle cross-section (FC), and fiber density and cross-section (FDC) - within predefined white matter tracts from the XTRACT atlas [39]. Single-voxel proton MRS (PRESS; TR = 2000 ms, TE = 30 ms) was acquired from the anterior cingulate cortex (ACC), caudate nucleus, prefrontal cortex (PFC), and thalamus, and metabolite concentrations were quantified with LCModel [40] referenced to an unsuppressed water signal and corrected for voxel tissue composition. Detailed acquisition parameters and processing pipelines are provided in Supplementary Methods (Supplemental File S1).

Statistical Analyses

Descriptive statistics (mean, median, standard deviation, and range) were calculated for continuous variables. Data normality was assessed using the Shapiro–Wilk test, and pairwise associations were evaluated using Pearson’s or Spearman’s correlation analyses, as appropriate. Linear mixed-effects (LME) models were used to examine the effects of olfactory group (individuals drinking alcohol with normal olfactory function [$TD \geq 16$] vs. with olfactory dysfunction [$TD < 16$]), odor concentration (8%, 13%, 25%, 37%, and 42.8%), and their interaction on familiarity, intensity, pleasantness, and craving ratings. Participant was included as a random intercept to account for repeated measurements. Odor concentration was modelled as a continuous variable for intensity and as a categorical variable for familiarity, pleasantness, and craving. Fixed-effect estimates (β), standard errors (SE), Wald z-statistics, and two-sided p-values were reported. In addition, relationships of TD score with behavioral measures, and individual structural MRI regions, diffusion MRI tract-specific measures, and MRS-derived metabolite concentrations were then assessed, along with their associations with alcohol consumption.

To reduce the dimensionality, Principal Component Analysis (PCA) was performed separately for predefined structural MRI, diffusion MRI, and MRS measures. The first principal component (PC1) from each modality was retained as a standardized composite score. The constituent measures entering each composite are listed in Supplemental Tables S1–S3 (Supplemental FileS1). Covariate-adjusted ordinary least squares (OLS) regression models then examined (i) the association between continuous alcohol consumption and olfactory TD score and composites of structural MRI, diffusion MRI, and MRS-derived metrics, (ii) the associations between the MRS composite and the structural MRI and diffusion MRI composite measures while adjusting for alcohol consumption. Additional regression analyses using the individual constituent measures identified the contributors driving each composite. All models were adjusted for age, smoking status, GAD-7, and PHQ-9 scores, with estimated total intracranial volume (eTIV) additionally included for volumetric MRI outcomes.

A mediation analysis examined whether the MR composites mediated the association between olfactory TD score and alcohol consumption. Indirect effects ($a \times b$) were estimated using nonparametric bootstrapping, and statistical significance was determined from bias-corrected 95% confidence intervals. Statistical significance was defined as a two-tailed $p < 0.05$. Where applicable, p-values were corrected for multiple comparisons using the false discovery rate (FDR) procedure.

Results

Demographics

Participant characteristics are summarized in Table 1. The study included 98 individuals drinking alcohol (drinks per drinking session: range 0–35 drinks, median 9.5), comprising 44 participants with olfactory dysfunction ($TD < 16$) and 54 with normal olfactory function ($TD \geq 16$). The two groups were comparable in age, body mass index, educational status, religion, family income, smoking status, and psychiatric

symptom severity (all $p > 0.05$). Compared with participants with normal olfactory function, those with olfactory dysfunction had lower MoCA scores ($p < 0.01$), greater nicotine dependence ($p = 0.04$), higher alcohol craving (PACS; $p < 0.01$), poorer olfactory threshold and discrimination scores (both $p < 0.001$), more drinking sessions in the previous 12 months ($p < 0.01$), and a greater maximum number of drinks consumed in the past year ($p = 0.01$). Age at first alcohol use and preferred alcoholic beverage did not differ between groups.

Alcohol Consumption and Self-reported Craving Is Associated with Olfactory Dysfunction

Greater alcohol consumption was associated with poorer olfactory function. Olfactory TD scores were negatively correlated with total alcohol consumption ($r = -0.23$, $p = 0.04$; Fig. 2B), the QF index ($r = -0.28$, $p < 0.01$; Fig. 2B), and cumulative lifetime alcohol exposure (age-adjusted log drink-years; partial $r = -0.37$, $p < 0.01$). Drinking duration was not associated with TD score, suggesting that olfactory dysfunction was related to cumulative alcohol exposure rather than duration alone. Consistent with this, cumulative lifetime alcohol exposure remained an independent predictor of lower TD scores after adjustment for age ($\beta = -0.38$, $p < 0.01$; Fig. 2B). Olfactory TD scores were also negatively associated with alcohol craving severity measured using the PACS ($r = -0.40$, $p < 0.01$; Fig. 2B).

Alcohol-related odor cues remain perceptually and motivationally salient despite olfactory dysfunction

Individuals drinking alcohol with olfactory dysfunction (OD; TD < 16) exhibited reduced familiarity with several non-alcohol odor categories but preserved familiarity for alcohol-related odors (Fig. 2C). Specifically, familiarity ratings were significantly lower for trigeminal ($\beta = -0.18$, $p = 0.01$) and appetitive odors ($\beta = -0.19$, $p = 0.02$), whereas familiarity with alcohol beverage ($\beta = -0.06$, $p = 0.61$), ethanol ($\beta = -0.18$, $p = 0.10$), and rose odors ($\beta = -0.14$, $p = 0.19$) did not differ between olfactory groups. Odor concentration had little influence on familiarity, except for lower familiarity with alcohol beverage odors at 25% ($p = 0.03$) and a significant group $\times$ concentration interaction for ethanol at 37% ($\beta = 0.36$, $p < 0.01$; Fig. 2D).

Perceived odor intensity increased with odor concentration across trigeminal, neutral, appetitive, and ethanol odor categories, whereas alcohol beverage odors showed a similar positive trend that did not reach statistical significance. Neither olfactory group nor the group $\times$ concentration interaction significantly influenced intensity ratings for any odor category. Nevertheless, participants with olfactory dysfunction gave alcohol beverage odors intensity ratings comparable to, and at higher concentrations numerically greater than, those of participants with normal olfactory function (Fig. 2E).

Pleasantness ratings were largely comparable between groups, with no significant main effects of olfactory group for any odor category (all $p > 0.26$). Appetitive odors were rated as more pleasant at the highest concentration at 42.8% ($\beta = 4.73$, $p = 0.03$), whereas ethanol pleasantness increased at 8% ($\beta = 6.50$, $p = 0.02$) and highest (42.8%; $\beta = 7.49$, $p = 0.01$) concentrations. However, participants with

olfactory dysfunction rated ethanol as significantly less pleasant than those with normal olfactory function at the 8% (interaction $\beta = -9.25, p = 0.04$) and 25% (interaction $\beta = -10.82, p = 0.02$) concentrations, with similar trends at 37% ($p = 0.07$) and 42.8% ($p = 0.08$). No significant interaction effects were observed for alcohol beverage odors (Fig. 2F).

Finally, alcohol beverage and ethanol odors were evaluated for their ability to evoke alcohol craving. Although neither the main effects of olfactory group nor odor concentration were significant, individuals drinking alcohol with olfactory dysfunction exhibited significantly greater craving in response to the highest concentration of alcohol beverage odors (42.8%; interaction $\beta = 0.67, p = 0.04$). In contrast, ethanol odors did not significantly influence craving, with no significant main or interaction effects (all $p > 0.26$; Fig. 2G; Table 2).

Table 2

Linear mixed-effects model comparing alcohol drinkers with normal olfactory function and alcohol drinkers with olfactory dysfunction across odor concentrations.

Odor Category	Concentration (%)	Intensity β (95% CI), p	Pleasantness β (95% CI), p	Familiarity β (95% CI), p	Craving β (95% CI), p
Alcohol beverages	8 (beer)	-0.21 (-1.31 to 0.88), $p = 0.70$	-1.48 (-11.53 to 8.58), $p = 0.77$	0.08 (-0.20 to 0.35), $p = 0.59$	0.10 (-0.54 to 0.75), $p = 0.75$
	13 (wine; Ref)	Reference	Reference	Reference	Reference
	25 (country liquor)	-0.09 (-1.18 to 1.01), $p = 0.87$	5.42 (-4.63 to 15.48), $p = 0.29$	0.13 (-0.14 to 0.41), $p = 0.34$	0.30 (-0.34 to 0.95), $p = 0.35$
	37 (whiskey)	0.12 (-0.97 to 1.21), $p = 0.82$	5.70 (-4.36 to 15.75), $p = 0.26$	-0.11 (-0.38 to 0.17), $p = 0.45$	0.27 (-0.37 to 0.92), $p = 0.40$
	42.8 (whiskey)	0.25 (-0.84 to 1.35), $p = 0.64$	1.36 (-8.69 to 11.41), $p = 0.79$	-0.09 (-0.37 to 0.18), $p = 0.50$	0.67 (0.02 to 1.32), $p = 0.04^*$
Ethanol	8	0.09 (-0.90 to 1.08), $p = 0.85$	-9.25 (-18.19 to -0.31), $p = 0.04^*$	-0.03 (-0.30 to 0.23), $p = 0.80$	0.18 (-0.58 to 0.93), $p = 0.64$
	13 (Ref)	Reference	Reference	Reference	Reference
	25	-0.07 (-1.06 to 0.93), $p = 0.89$	-10.82 (-19.77 to -1.88), $p = 0.01^*$	0.06 (-0.21 to 0.32), $p = 0.67$	0.37 (-0.38 to 1.11), $p = 0.33$
	37	0.49 (-0.50 to 1.48), $p = 0.33$	-8.29 (-17.24 to 0.65), $p = 0.06$	0.36 (0.09 to 0.62), $p = 0.01^{**}$	0.39 (-0.37 to 1.14), $p = 0.31$

Notes: Linear mixed-effects models compared alcohol drinkers with normal olfactory function ($TD \geq 16$) and alcohol drinkers with olfactory dysfunction ($TD < 16$). Values represent the group $\times$ concentration interaction estimates (β) with 95% confidence intervals (CI), using 13% concentration as the reference level. Positive β values indicate higher ratings in the olfactory dysfunction group relative to the normal olfactory function group at the corresponding concentration. Participant was included as a random intercept to account for repeated measurements. Intensity, pleasantness, familiarity, and craving were analyzed separately for each odor category. Alcohol craving was assessed only for alcohol beverage and ethanol odors. Abbreviations: TD, threshold–discrimination score; CI, confidence interval. $p < 0.05$; $p < 0.01$.

Odor Category	Concentration (%)	Intensity β (95% CI), p	Pleasantness β (95% CI), p	Familiarity β (95% CI), p	Craving β (95% CI), p
	42.8	-0.27 (-1.26 to 0.73), $p = 0.59$	-7.99 (-16.93 to 0.95), $p = 0.08$	-0.08 (-0.35 to 0.19), $p = 0.54$	0.43 (-0.32 to 1.18), $p = 0.26$
Trigeminal (clove, mint, cinnamon)	8	0.19 (-0.54 to 0.92), $p = 0.61$	-2.34 (-8.56 to 3.87), $p = 0.46$	0.11 (-0.04 to 0.26), $p = 0.14$	—
	13 (Ref)	Reference	Reference	Reference	Reference
	25	0.27 (-0.46 to 1.00), $p = 0.47$	-3.51 (-9.72 to 2.71), $p = 0.26$	0.09 (-0.05 to 0.24), $p = 0.20$	—
	37	-0.33 (-1.07 to 0.40), $p = 0.37$	-3.07 (-9.29 to 3.14), $p = 0.33$	0.10 (-0.05 to 0.24), $p = 0.20$	—
	42.8	0.14 (-0.59 to 0.87), $p = 0.70$	-1.96 (-8.17 to 4.26), $p = 0.53$	0.09 (-0.06 to 0.24), $p = 0.24$	—
Appetitive (banana, vanilla)	8	0.26 (-0.50 to 1.03), $p = 0.49$	-4.38 (-11.07 to 2.32), $p = 0.20$	0.10 (-0.09 to 0.30), $p = 0.29$	—
	13 (Ref)	Reference	Reference	Reference	Reference
	25	0.17 (-0.59 to 0.93), $p = 0.66$	-5.35 (-12.05 to 1.34), $p = 0.11$	0.09 (-0.10 to 0.29), $p = 0.33$	—
	37	0.01 (-0.75 to 0.77), $p = 0.97$	1.53 (-5.17 to 8.23), $p = 0.65$	0.05 (-0.15 to 0.24), $p = 0.62$	—

Notes: Linear mixed-effects models compared alcohol drinkers with normal olfactory function ($TD \geq 16$) and alcohol drinkers with olfactory dysfunction ($TD < 16$). Values represent the group $\times$ concentration interaction estimates (β) with 95% confidence intervals (CI), using 13% concentration as the reference level. Positive β values indicate higher ratings in the olfactory dysfunction group relative to the normal olfactory function group at the corresponding concentration. Participant was included as a random intercept to account for repeated measurements. Intensity, pleasantness, familiarity, and craving were analyzed separately for each odor category. Alcohol craving was assessed only for alcohol beverage and ethanol odors. Abbreviations: TD, threshold–discrimination score; CI, confidence interval. $p < 0.05$; $p < 0.01$.

Odor Category	Concentration (%)	Intensity β (95% CI), p	Pleasantness β (95% CI), p	Familiarity β (95% CI), p	Craving β (95% CI), p
	42	0.09 (-0.67 to 0.85), $p = 0.81$	-5.56 (-12.26 to 1.13), $p = 0.10$	-0.00 (-0.19 to 0.19), $p = 0.98$	—
Neutral (PEA/Rose)	8	-0.11 (-1.05 to 0.82), $p = 0.81$	-4.93 (-13.33 to 3.48), $p = 0.25$	0.03 (-0.23 to 0.30), $p = 0.80$	—
	13 (Ref)	Reference	Reference	Reference	Reference
	25	-0.69 (-1.62 to 0.25), $p = 0.15$	-7.79 (-16.19 to 0.61), $p = 0.06$	-0.06 (-0.33 to 0.21), $p = 0.67$	—
	37	-0.23 (-1.17 to 0.70), $p = 0.62$	-6.12 (-14.53 to 2.28), $p = 0.15$	0.08 (-0.18 to 0.35), $p = 0.53$	—
	42.8	-0.36 (-1.29 to 0.58), $p = 0.45$	-5.16 (-13.56 to 3.24), $p = 0.22$	0.05 (-0.21 to 0.32), $p = 0.69$	—

Notes: Linear mixed-effects models compared alcohol drinkers with normal olfactory function ($TD \geq 16$) and alcohol drinkers with olfactory dysfunction ($TD < 16$). Values represent the group $\times$ concentration interaction estimates (β) with 95% confidence intervals (CI), using 13% concentration as the reference level. Positive β values indicate higher ratings in the olfactory dysfunction group relative to the normal olfactory function group at the corresponding concentration. Participant was included as a random intercept to account for repeated measurements. Intensity, pleasantness, familiarity, and craving were analyzed separately for each odor category. Alcohol craving was assessed only for alcohol beverage and ethanol odors. Abbreviations: TD, threshold–discrimination score; CI, confidence interval. $p < 0.05$; $p < 0.01$.

Olfactory Dysfunction Is Associated with Cognitive Performance and Multimodal Brain Alterations

We next examined relationships between TD score and cognitive performance and multimodal neuroimaging measures. Higher TD scores were associated with better global cognitive performance (MoCA; $r = 0.23$, $p = 0.03$, $n = 87$; Fig. 2B).

Poorer olfactory function was associated with widespread structural, microstructural, and neurochemical abnormalities. Following FDR correction, higher TD scores were associated with greater orbitofrontal cortex (OFC) cortical thickness ($r = 0.40$, $pFDR < 0.01$), larger thalamic ($r = 0.40$, $pFDR < 0.01$), pallidal ($r = 0.33$, $pFDR = 0.02$), olfactory tubercle ($r = 0.30$, $pFDR = 0.03$), putamen ($r = 0.29$, $pFDR = 0.03$), anterior olfactory nucleus ($r = 0.27$, $pFDR = 0.03$), and amygdala ($r = 0.25$, $pFDR = 0.04$) volumes.

Fixel-based diffusion analyses demonstrated significant associations with fibre cross-section (logFC; $r = 0.52$, $pFDR < 0.01$) and fibre density and cross-section (FDC; $r = 0.44$, $pFDR < 0.01$) within the superior thalamic radiation, together with additional associations involving the uncinate fasciculus, cingulum bundle, anterior thalamic radiation, and inferior fronto-occipital fasciculus. Higher TD scores were also associated with greater prefrontal glutamate ($r = 0.38$, $pFDR < 0.01$) and NAA concentrations ($r = 0.31$, $pFDR = 0.04$). In addition, greater alcohol consumption was associated with higher PACS scores ($\rho = 0.55$, $pFDR < 0.01$) and lower superior frontal cortical thickness ($\rho = -0.40$, $pFDR < 0.01$).

To determine whether these findings were independent of potential confounders, multivariable regression analyses were adjusted for age, smoking status, GAD-7, and PHQ-9 scores. Higher TD scores remained independently associated with greater OFC cortical thickness ($\beta = 0.35$, $pFDR = 0.02$), thalamic volume ($\beta = 0.45$, $pFDR = 0.04$), superior thalamic radiation fibre cross-section (logFC; $\beta = 0.49$, $pFDR < 0.01$) and fibre density and cross-section (FDC; $\beta = 0.41$, $pFDR = 0.01$), uncinate fasciculus logFC ($\beta = 0.34$, $pFDR = 0.04$), cingulum bundle FDC ($\beta = 0.33$, $pFDR = 0.05$), and prefrontal glutamate ($\beta = 0.37$, $pFDR < 0.01$) and NAA concentrations ($\beta = 0.26$, $pFDR = 0.03$) (Fig. 3A). Associations with inferior fronto-occipital fasciculus FDC ($\beta = 0.31$, $p = 0.02$), anterior thalamic radiation FDC ($\beta = 0.29$, $p = 0.03$), and uncinate fasciculus FDC ($\beta = 0.28$, $p = 0.05$) were nominally significant but did not survive false discovery rate correction (Fig. 3A).

We then compared individuals drinking alcohol with and without olfactory dysfunction across multiple brain metrics. The olfactory dysfunction group showed lower MoCA scores ($d = -0.58$, $pFDR = 0.02$), thalamic ($d = -0.70$, $pFDR = 0.01$) and amygdala volumes ($d = -0.67$, $pFDR = 0.01$), superior thalamic radiation fibre cross-section (logFC; $d = -1.30$, $pFDR < 0.001$) and fibre density and cross-section (FDC; $d = -1.19$, $pFDR < 0.001$), and prefrontal glutamate concentration ($d = -0.78$, $pFDR = 0.01$). OFC ($d = -0.56$), superior frontal ($d = -0.61$), rostral middle frontal ($d = -0.53$), and pars orbitalis ($d = -0.60$) cortical thickness, ACC cortical thickness ($d = -0.35$), and ACC NAA ($d = -0.47$) and glutamate ($d = -0.58$) concentrations were also numerically lower in the olfactory dysfunction group but did not survive false discovery rate correction (Table 3).

Table 3

Comparison of cognitive performance and brain metrics between alcohol drinkers with normal olfactory function and olfactory dysfunction

Domain	Brain metric	Normal olfactory function Mean $\pm$ SD	Olfactory dysfunction Mean $\pm$ SD	Effect size (β or cohen's d)	95% CI	P / pFDR
Cognition	MOCA	21.87 $\pm$ 4.87	19.12 $\pm$ 4.42	-0.58	[-1.02, -0.15]	0.01 / 0.02
Cortical thickness (mm)	Orbitofrontal cortex	2.68 $\pm$ 0.13	2.61 $\pm$ 0.12	-0.56	[-1.04, -0.08]	0.01 / 0.05
	Superior frontal cortex	2.72 $\pm$ 0.15	2.64 $\pm$ 0.13	-0.61	[-1.10, -0.13]	0.01 / 0.05
	Rostral middle frontal cortex	2.48 $\pm$ 0.14	2.41 $\pm$ 0.09	-0.53	[-1.01, -0.06]	0.02 / 0.05
	Anterior cingulate cortex	2.67 $\pm$ 0.13	2.62 $\pm$ 0.14	-0.35	[-0.82, 0.11]	0.13 / 0.16
	Pars orbitalis	2.75 $\pm$ 0.17	2.66 $\pm$ 0.12	-0.60	[-1.08, -0.12]	0.01 / 0.05
Subcortical volume (mm ³)	Thalamus	13842.28 $\pm$ 1092.35	13005.86 $\pm$ 1275.26	-0.70	[-1.18, -0.22]	0.004 / 0.01
	Amygdala	3660.41 $\pm$ 217.87	3467.78 $\pm$ 340.87	-0.67	[-1.15, -0.19]	0.01 / 0.01
Diffusion MRI	Superior thalamic radiation (fc)	0.09 $\pm$ 0.05	0.02 $\pm$ 0.06	-1.30	[-1.89, -0.72]	< .001 / < .001
	Superior thalamic radiation (fdc)	0.47 $\pm$ 0.03	0.43 $\pm$ 0.04	-1.19	[-1.77, -0.61]	< .001 / < .001
Magnetic resonance spectroscopy (mmol/kg)	ACC-NAA	11.93 $\pm$ 2.13	10.68 $\pm$ 3.05	-0.47	[-0.95, 0.01]	0.05 / 0.11
	PFC Glutamate	14.80 $\pm$ 1.82	13.30 $\pm$ 1.96	-0.78	[-1.28, -0.29]	0.002 / 0.01

Notes: Data are presented as mean $\pm$ standard deviation (SD). Group differences were quantified using Cohen's d for unadjusted comparisons. Positive values indicate higher measures in participants with normal olfactory function, whereas negative values indicate lower measures in participants with olfactory dysfunction. Ninety-five percent confidence intervals (95% CI) are reported for effect sizes. P values represent unadjusted comparisons, and pFDR values denote Benjamini–Hochberg false discovery rate-adjusted P values within each imaging modality. Abbreviations: ACC, anterior cingulate cortex; FC, fibre cross-section; FDC, fibre density and cross-section; MoCA, Montreal Cognitive Assessment; NAA, N-acetylaspartate; PFC, prefrontal cortex.

Domain	Brain metric	Normal olfactory function Mean ± SD	Olfactory dysfunction Mean ± SD	Effect size (β or cohen's d)	95% CI	P / pFDR
	ACC Glutamate	17.61 ± 3.54	15.12 ± 4.90	-0.58	[-1.06, -0.10]	0.01 / 0.07
Notes: Data are presented as mean ± standard deviation (SD). Group differences were quantified using Cohen's d for unadjusted comparisons. Positive values indicate higher measures in participants with normal olfactory function, whereas negative values indicate lower measures in participants with olfactory dysfunction. Ninety-five percent confidence intervals (95% CI) are reported for effect sizes. P values represent unadjusted comparisons, and pFDR values denote Benjamini–Hochberg false discovery rate-adjusted P values within each imaging modality. Abbreviations: ACC, anterior cingulate cortex; FC, fibre cross-section; FDC, fibre density and cross-section; MoCA, Montreal Cognitive Assessment; NAA, N-acetylaspartate; PFC, prefrontal cortex.						

Principal Component Analysis Identifies Latent Structural and Neurochemical Components

PCA was performed separately for each imaging modality to derive composite measures for subsequent analyses (Fig. 3B; Supplemental Tables S1-S3). For proton MRS, the first principal component (PC1) explained 44.1% of the variance ($n = 75$; Cronbach's $\alpha = 0.70$), with ACC NAA+NAAG and NAA showing the highest loadings (0.90 and 0.85, respectively; Fig. 3B). For structural MRI, PC1 explained 58.3% of the variance ($n = 74$; Cronbach's $\alpha = 0.62$; Fig. 3B), with the AON and OT contributing most strongly. For diffusion MRI, PC1 explained 74.0% of the variance ($n = 61$; Cronbach's $\alpha = 0.93$), with consistently high loadings (0.75–0.92) across all six white matter tracts (Fig. 3B).

Alcohol Consumption Is Associated with Neurometabolic, Gray Matter, and White Matter Components

Greater alcohol consumption was associated with the MRS composite score (standardized $\beta = 0.52$, $p < 0.01$; bootstrap 95% CI: 0.24–0.83; permutation $p < 0.01$; $n = 61$), indicating lower neurometabolite concentrations with increasing alcohol intake. In turn, the MRS composite was significantly associated with both the structural MRI composite representing olfactory cortical regions (standardized $\beta = 0.38$, $p < 0.01$; bootstrap 95% CI: 0.05–0.62; permutation $p < 0.01$; $n = 58$) and the diffusion MRI composite (standardized $\beta = 0.44$, $p < 0.01$; bootstrap 95% CI: 0.07–0.86; permutation $p < 0.01$; $n = 48$) (Fig. 3C). These associations remained robust in Huber regression and jackknife leave-one-out sensitivity analyses.

Neurometabolite Alterations Mediate the Association Between Olfactory Dysfunction and Alcohol Consumption

Although olfactory TD score was not directly associated with the MRS composite (standardized $\beta = -0.27$, $p = 0.06$; $n = 59$), alcohol consumption remained significantly associated with the MRS composite

after adjustment for TD score (standardized $\beta = 0.41$, $p < 0.01$; $n = 59$). Bootstrap mediation analysis identified a significant indirect effect of olfactory TD score on alcohol consumption through the MRS composite (indirect effect = -0.11 , 95% bootstrap CI: -0.25 to -0.02 ; Fig. 3D), indicating partial mediation. The structural MRI and diffusion MRI components were subsequently decomposed into their constituent regions and white matter tracts.

Region-wise and Tract-wise Decomposition of Multimodal Components

The structural MRI component was mainly driven by the anterior olfactory nucleus ($\beta = -0.32$, $p < 0.01$, $pFDR = 0.03$) and olfactory tubercle ($\beta = -0.31$, $p = 0.03$, $pFDR = 0.04$). The diffusion MRI component was chiefly explained by fibre cross-section and fibre density and cross-section in the forceps minor ($\beta = 0.50$, $p < 0.01$, $pFDR < 0.01$) and superior thalamic radiation ($\beta = 0.40$, $p < 0.01$, $pFDR = 0.02$), with additional contributions from the uncinate fasciculus ($\beta = 0.39$, $p = 0.01$, $pFDR = 0.02$), cingulum bundle ($\beta = 0.46$, $p < 0.01$, $pFDR = 0.02$), and anterior thalamic radiation ($\beta = 0.38$, $p = 0.01$, $pFDR = 0.02$) (Fig. 3E). Overall, these results localize the multimodal associations primarily to interconnected olfactory and frontolimbic reward pathways.

Discussion

The present study provides multimodal evidence that chronic alcohol consumption is associated with progressive olfactory dysfunction accompanied by coordinated structural, microstructural, and neurometabolic alterations within an olfactory–reward network. Although increasing alcohol consumption was associated with poorer olfactory function, individuals drinking alcohol with olfactory dysfunction retained familiarity, suprathreshold intensity perception, and cue-induced craving for alcohol beverage odors. Furthermore, olfactory dysfunction was associated with widespread abnormalities in gray matter, white matter, and neurometabolite integrity, while neurometabolic alterations partially mediated the relationship between olfactory dysfunction and alcohol consumption, suggesting a potential biological mechanism linking chronic alcohol exposure to progressive impairment of olfactory–reward circuitry.

Olfactory dysfunction was further associated with poorer global cognitive performance and widespread abnormalities across multiple levels of brain organization, including reduced cortical thickness within orbitofrontal, anterior cingulate, superior frontal, and rostral middle frontal cortices, reduced volumes of the amygdala and thalamus, compromised white matter integrity within the superior thalamic radiation, and lower concentrations of neuronal and glutamatergic metabolites, including NAA and glutamate within prefrontal and anterior cingulate regions. PCA further demonstrated coordinated relationships among neurometabolic, gray matter, and white matter components, with higher alcohol consumption associated with lower neurometabolite integrity that, in turn, was related to alterations in olfactory cortical regions and distributed frontolimbic white matter pathways. Importantly, neurometabolic alterations significantly mediated the association between olfactory dysfunction and alcohol

consumption, suggesting that metabolic dysfunction may represent a key neurobiological mechanism linking progressive olfactory impairment with widespread structural brain alterations in chronic alcohol use.

One of the principal findings of this study is the dissociation between impaired general olfactory function and preserved responsiveness to alcohol-related odor cues. Although individuals drinking alcohol with olfactory dysfunction demonstrated reduced familiarity with trigeminal and appetitive odors, familiarity with alcohol beverage odors remained intact. Likewise, suprathreshold intensity perception did not differ between olfactory groups, indicating preserved perceptual processing of alcohol-related odors despite impaired odor detection. Most importantly, individuals drinking alcohol with olfactory dysfunction exhibited greater cue-induced craving in response to the highest concentration of alcohol beverage odors, whereas pure ethanol odors did not produce comparable effects. These findings suggest that chronic alcohol exposure selectively preserves the perceptual and motivational salience of learned alcohol beverage cues rather than producing a generalized impairment of olfactory processing. This observation is consistent with incentive sensitization theory[41], whereby repeated alcohol exposure enhances the motivational salience of alcohol-associated cues even as sensory function deteriorates.

The widespread neuroimaging alterations associated with olfactory dysfunction suggest that impaired olfactory function in chronic alcohol use reflects disruption of distributed olfactory–reward networks rather than isolated dysfunction of the primary olfactory system. Consistent with previous studies of alcohol use disorder, poorer olfactory performance was associated with reduced cortical thickness in the orbitofrontal, anterior cingulate, superior frontal, and rostral middle frontal cortices, together with smaller amygdala and thalamic volumes [42]. These regions are central to odor perception [12], reward valuation [43], salience processing [43], and executive control, indicating that alcohol-related olfactory dysfunction extends beyond sensory impairment to involve higher-order cognitive and motivational processes. Supporting this interpretation, poorer olfactory function was also associated with lower global cognitive performance, suggesting that olfactory dysfunction may serve as an accessible behavioral marker of widespread frontolimbic network degeneration in chronic alcohol use.

Our diffusion MRI findings indicate that alcohol-related olfactory dysfunction is accompanied by disruption of white matter pathways linking olfactory, limbic, and executive networks. Poorer olfactory function was associated with reduced fibre cross-section and fibre density within the superior thalamic radiation, with additional contributions from the uncinate fasciculus, cingulum bundle, anterior thalamic radiation, inferior fronto-occipital fasciculus, and forceps minor. Although the primary olfactory pathway bypasses the thalamus, thalamic projections are critical for integrating olfactory information with attentional and prefrontal networks [44, 45]. Accordingly, these findings suggest that alcohol-related olfactory dysfunction reflects impaired network communication rather than dysfunction confined to primary olfactory regions. Together with previous reports of widespread white matter abnormalities in alcohol use disorder [46], our results support the concept that chronic alcohol exposure disrupts a distributed frontolimbic connectome linking odor perception with reward processing, providing a structural substrate for preserved alcohol cue salience despite declining olfactory sensitivity.

Beyond structural alterations, neurometabolic abnormalities emerged as a central feature of the observed network dysfunction. Better olfactory performance was associated with higher prefrontal concentrations of NAA and glutamate, suggesting that olfactory dysfunction is accompanied by reduced neuronal integrity and excitatory neurotransmission. NAA is widely regarded as a marker of neuronal viability and metabolic function [47], whereas glutamate is the principal excitatory neurotransmitter underlying cortical communication and synaptic plasticity [48]. Chronic alcohol exposure has consistently been linked to disturbances in glutamatergic signaling and neuronal metabolism [49], and our findings suggest that these neurochemical alterations are closely related to behavioral measures of olfactory dysfunction. Consistent with this, principal component analysis demonstrated that alcohol consumption was associated with a latent neurometabolic component, which was subsequently associated with both gray matter and white matter components, supporting the concept that metabolic dysfunction accompanies coordinated structural alterations across interconnected olfactory–reward circuits.

Mediation analysis provided further insight into these relationships by demonstrating a significant indirect effect of olfactory dysfunction on alcohol consumption through the neurometabolic component. Although the cross-sectional design precludes causal inference, these findings are consistent with experimental evidence that chronic alcohol exposure disrupts neuronal metabolism and glutamatergic signalling before the development of widespread structural degeneration. Together, our results suggest that neurometabolic dysfunction may represent an intermediate mechanism linking chronic alcohol exposure with multimodal brain alterations and behavioral olfactory impairment.

A major strength of this study is the integration of comprehensive olfactory phenotyping with multimodal neuroimaging. By combining structural MRI, diffusion MRI, and ^1H -MRS within the same cohort, we demonstrate that alcohol-related olfactory dysfunction is associated with coordinated alterations in cortical morphology, white matter integrity, and neuronal metabolism, implicating a distributed olfactory–reward network rather than isolated brain regions. These findings suggest that quantitative olfactory assessment may provide a simple, non-invasive behavioral marker of alcohol-related brain dysfunction. Moreover, the preservation of alcohol cue salience despite impaired olfactory function may help explain the persistence of cue-induced craving and highlights olfactory cue processing as a potential therapeutic target for cue-exposure, olfactory training, and virtual reality-based interventions.

This study has several limitations. First, its cross-sectional design precludes causal inference regarding the temporal sequence of neurometabolic, structural, and behavioral alterations. Second, only male participants were included, limiting generalizability to women. Third, imaging sample sizes differed across modalities because of data availability, although sensitivity analyses supported the robustness of the findings. Furthermore, the estimation of cumulative lifetime alcohol exposure assumes that participants' reported drinking patterns were relatively stable over their drinking history. This approach may not fully capture temporal fluctuations in alcohol consumption, including periods of heavier or lighter drinking, and may therefore introduce some uncertainty into estimates of cumulative lifetime exposure. Finally, while principal component analysis improved statistical power by reducing

dimensionality, validation of the derived imaging components in independent cohorts is warranted. Because alcohol consumption and diagnostic status are inherently correlated, all primary analyses were additionally adjusted for diagnostic group and repeated within diagnostic subgroups, with significant associations remaining robust where reported.

Conclusion

Our findings demonstrate that chronic alcohol consumption is associated with progressive olfactory dysfunction accompanied by coordinated neurometabolic, gray matter, and white matter alterations across the olfactory–reward network. Despite declining olfactory sensitivity, alcohol-related odors continue to evoke preserved perceptual and motivational responses, indicating a dissociation between sensory impairment and alcohol cue salience. Together, these findings suggest that multimodal dysfunction within olfactory–reward circuitry represents a shared neurobiological mechanism linking chronic alcohol exposure, olfactory dysfunction, and alcohol cue responsiveness.

Declarations

Financial disclosure

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Conflict of Interest Statement

Authors report no conflicts.

Author Contributions

KA conceived and designed the study. KA, RK, TB, AJ, AS, and AH recruited participants and collected the data. KA, RK, TB, AJ, and RR performed the data analyses and prepared the initial manuscript draft. KA interpreted the findings and critically reviewed and revised the manuscript. All authors (TB, RK, AJ, RR, AS, JA, SS, YPSB, and KA) reviewed the manuscript, contributed to its intellectual content, and approved the final version for publication.

Code Availability

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Figures

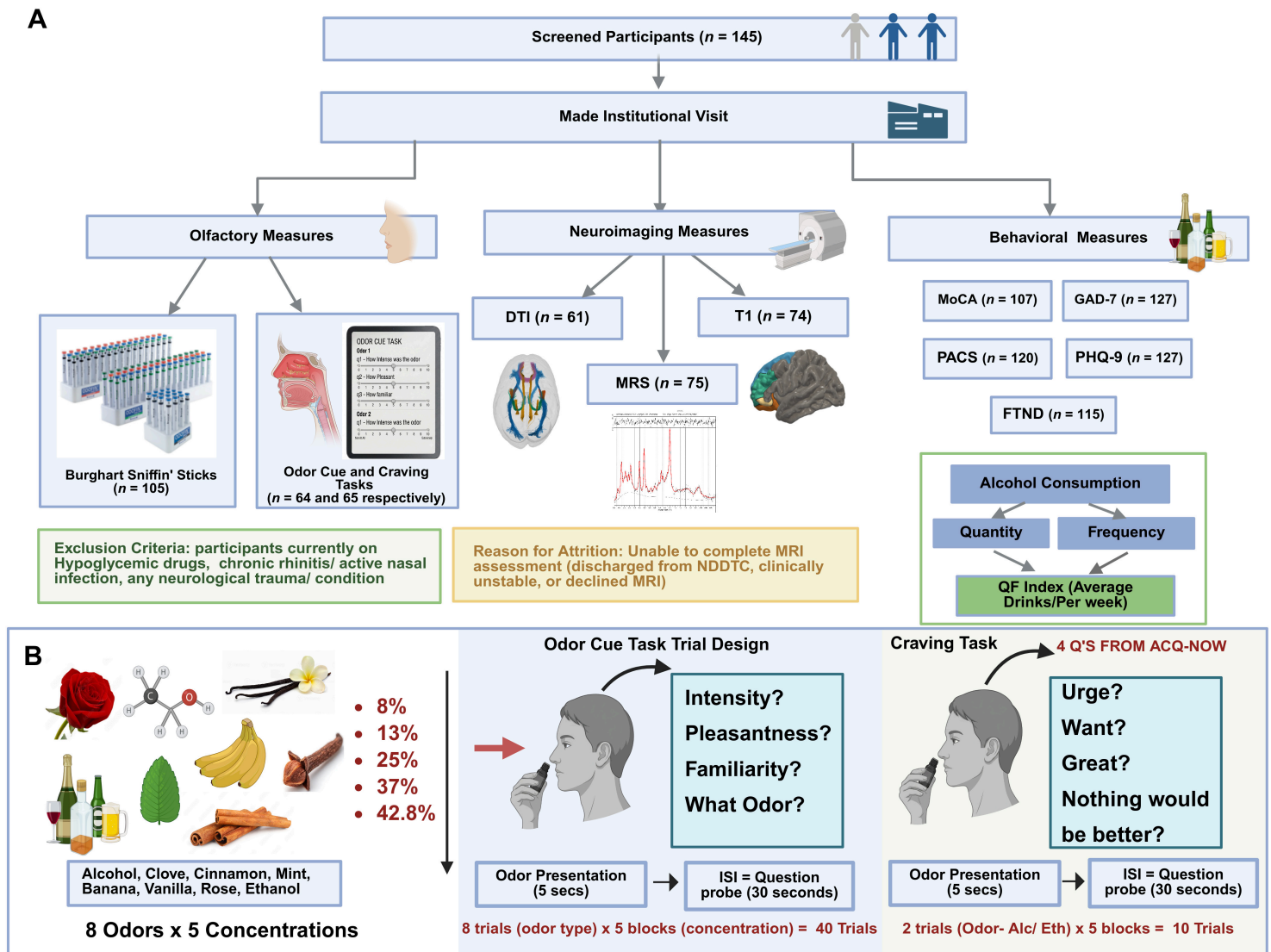


Figure 1

Study design and odor-cue paradigm. (A) Study flow. Of 145 individuals screened, those attending an institutional visit completed olfactory, neuroimaging and behavioral assessment; exclusion criteria and reasons for attrition are shown. For neuroimaging, n is the number of datasets that were analysed; for olfactory and behavioral measures, n is the number of participants who underwent the assessment. Alcohol quantity and frequency were combined into the quantity–frequency (QF) index (average drinks per week). (B) Odor-cue and craving task. Eight odorants were presented at five concentrations (8–42.8% v/v; 40 trials), each for 5 s with a ~30 s inter-stimulus interval during which participants rated intensity (visual analog scale [VAS] 0–10), pleasantness (VAS 0–100), familiarity (yes/no) and odor identity. Craving was then assessed for alcohol beverage and ethanol odors only (10 trials) using four items adapted from the Alcohol Craving Questionnaire–Now (ACQ-NOW).

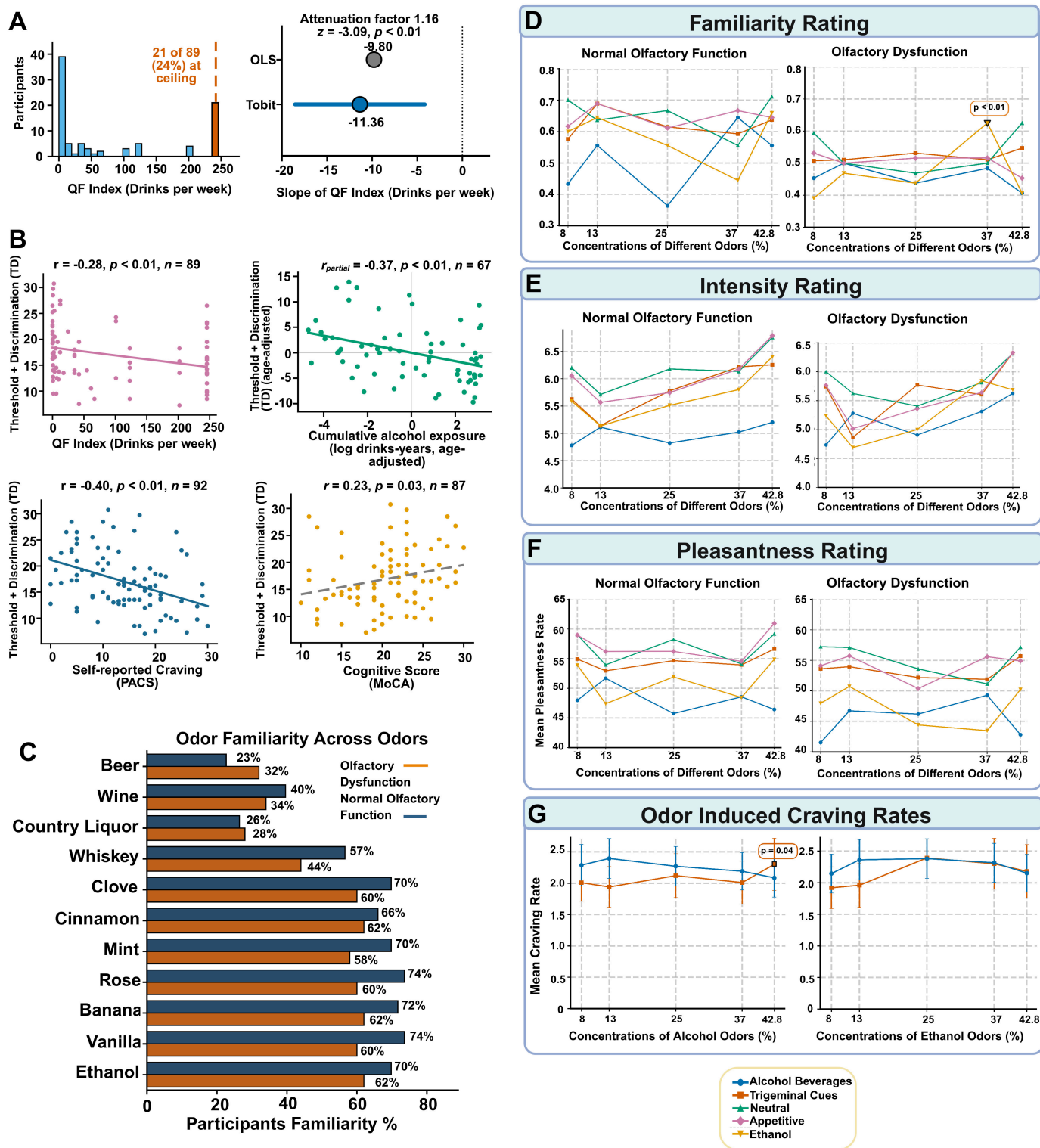


Figure 2

Alcohol consumption, olfactory function, cognitive performance and behavioral responses to odor cues. (A) Distribution of weekly alcohol consumption (QF index); the dashed line marks the censoring limit at which 24% of participants were capped. Right, ordinary least squares (OLS) and censored-normal (Tobit) estimates of the change in weekly consumption per unit olfactory threshold–discrimination (TD) score. (B) Associations of TD score with weekly alcohol consumption, age-adjusted cumulative exposure

(log drink-years), self-reported craving (Penn Alcohol Craving Scale, PACS) and global cognition (Montreal Cognitive Assessment, MoCA); lines are linear regression fits. (C) Percentage of participants familiar with each odorant, in participants with normal olfactory function (navy) and olfactory dysfunction (orange). D-F, mean familiarity (D), intensity (E) and pleasantness (F) ratings across concentrations, shown separately for normal olfactory function (left) and olfactory dysfunction (right); line colour denotes odor category (key at foot of figure). (G) Mean cue-induced craving across concentrations for alcohol beverage (left) and ethanol (right) odors, in participants with normal olfactory function (blue) and olfactory dysfunction (orange). Data are Mean $\pm$ SEM; statistics are reported in the Results and Table 1.

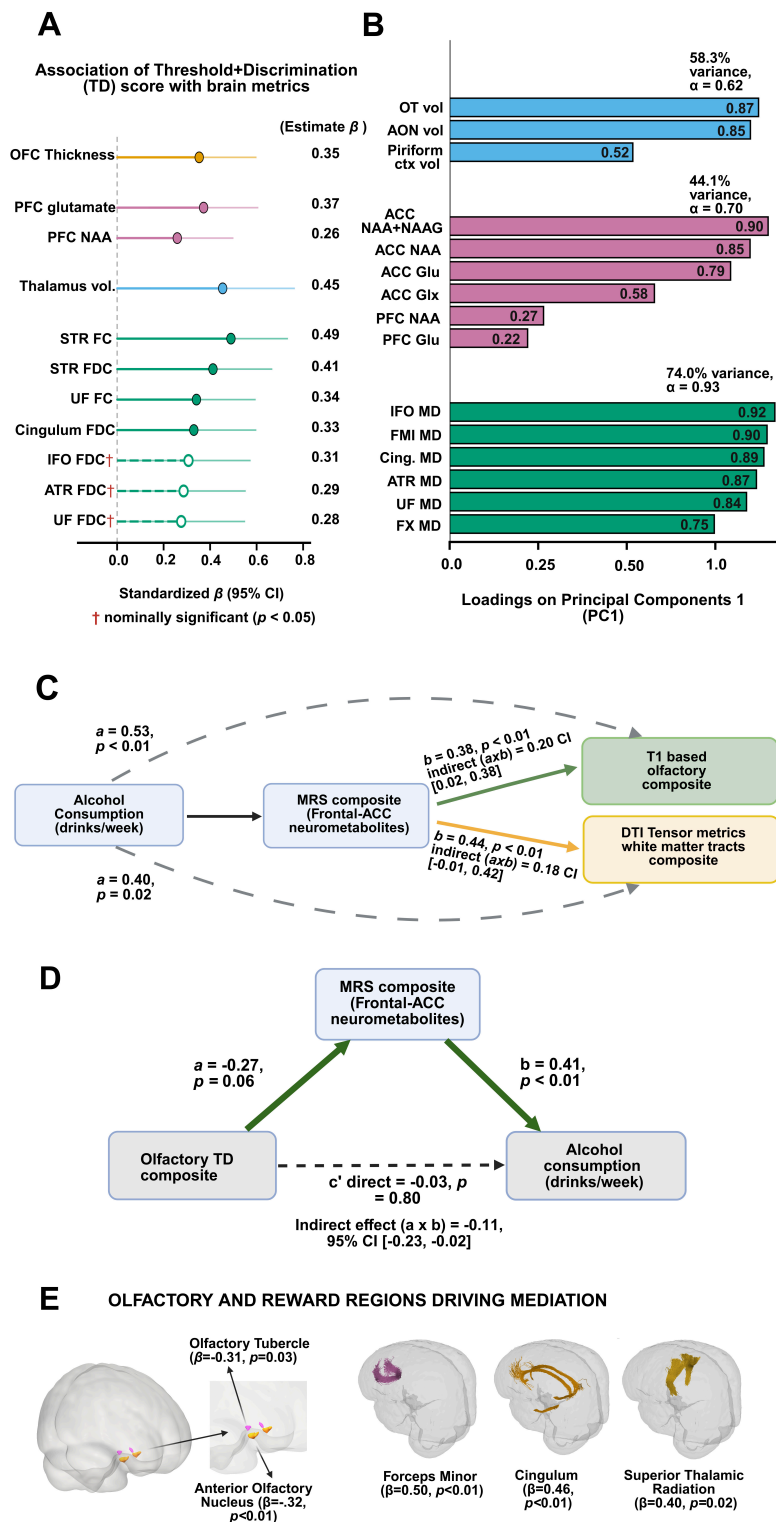


Figure 3

Multimodal brain correlates of olfactory function and mediation of the alcohol-olfaction relationship.

(A) Covariate-adjusted standardized regression coefficients ($\beta \pm 95\%$ confidence interval) for associations between olfactory TD score and orbitofrontal cortex (OFC) thickness, prefrontal cortex (PFC) ^1H -MRS metabolites, thalamic volume, and fibre cross-section (FC) and fibre density and cross-section (FDC) of frontolimbic tracts (STR, superior thalamic radiation; ATR, anterior thalamic radiation;

UF, uncinate fasciculus; IFO, inferior fronto-occipital fasciculus), adjusted for age, nicotine dependence, anxiety, depressive symptoms and – for volumetric measures – estimated total intracranial volume. Filled symbols survived Benjamini–Hochberg false discovery rate correction; open symbols (†) were nominally significant ($p < 0.05$) only. (B) Loadings of structural MRI volumes (blue), neurometabolites (pink) and diffusion MRI mean diffusivity measures (green) on the first principal component (PC1) of each modality, with variance explained and Cronbach's α . (C) Mediation of the association between alcohol consumption and each downstream brain composite by the neurometabolite (MRS) composite. (D) Reverse specification, with the olfactory TD composite predicting alcohol consumption through the MRS composite. In **C** and **D**, standardized path coefficients and bootstrapped indirect effects (5,000 resamples, 95% confidence interval) are shown on the diagram; all models were adjusted for age, nicotine dependence, anxiety and depressive symptoms. **e**, Region- and tract-wise decomposition showing the olfactory and frontolimbic structures driving the mediation, each with its standardized coefficient.

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