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Early abstinence in severe alcohol use disorder: MCP-1 decline, choroid plexus shrinkage, and region-specific grey-matter volume changes

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In this longitudinal study, 37 patients with severe alcohol use disorder (SAUD) were tested at the beginning (T1) and end (T2) of supervised detoxification to explore the evolution of and relationship between systemic inflammation, volumetric changes for brain grey matter (GM) and choroid plexus (ChP), and clinical symptoms. At T1, patients exhibited high levels of anxiety, depression, and craving, and had elevated plasmatic pro-inflammatory cytokines, indicating low-grade systemic inflammation. Monocyte chemoattractant protein-1 (CCL2) (MCP-1) levels correlated positively with ChP volume and severity of withdrawal symptoms, while macrophage inflammatory protein-1 beta (CCL4) (MIP-1β) also correlated with ChP volume, together suggesting an acute immune response at T1, and underscoring the ChP as a potential neuroimmune biomarker to be further evaluated in future studies. During three weeks' abstinence, Interleukin-8 (IL-8), MIP-1β, and MCP-1 levels decreased, although MIP-1β did not return to control levels, and tumor necrosis factor-alpha (TNF-α) showed no significant reduction. Volumetric MRI analyses suggested two concurrent trajectories during detoxification. First, an overall "recovery-driven" pattern of rapidly increasing GM volume in widespread forebrain regions with parallel declines in ventricle size and craving. Second, GM in limbic cortical areas, temporal and inferior frontal cortex showed no significant volumetric gain. However, these regional volumes correlated significantly with declining MCP-1, indicative of a "deflation", potentially related to declining microglial activation. These findings highlight the role of inflammatory processes in shaping early neuroplastic changes during detoxification and point to a central role of MCP-1 in inflammation-driven morphometric changes.

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INTRODUCTION

Severe alcohol use disorder (SAUD) is a major cause of preventable disability and mortality. Beyond its effects on brain structure and neurotransmission [1], increasing evidence implicates neuro-inflammation in alcohol-related brain damage [2].

In SAUD, inflammation encompasses systemic immune activation (e.g., elevated tumor necrosis factor-alpha -TNF-α-, IL-6 due to gut-derived endotoxins), neuroinflammation (glial activation in the central nervous system (CNS)), and microgliosis (a more specific microglial response involving morphological and functional shifts). These processes, often co-occurring, may interact through gut-brain and blood-brain barrier (BBB) dysfunction to exacerbate CNS injury [2].

Animal studies show that chronic alcohol exposure activates microglia, upregulates TLRs, and increases proinflammatory cytokines (e.g., IL-1β, TNF-α, MCP-1) in the hippocampus and prefrontal cortex, contributing to structural and cognitive impairments [3, 4]. Human post-mortem studies corroborate these findings, with increased microglial markers and proinflammatory signaling in the cingulate cortex, amygdala, ventral tegmental area, and orbitofrontal cortex of individuals with SAUD [5–7]. Notably, Crews et al. [5] identified a phagocytic-like microglial phenotype in the orbitofrontal cortex (upregulated Iba1, CD11b, CCR2, and reduced Tmem119, SOCS3) and showed that microglial blockade in alcohol-exposed mice blunted astrocyte reactivity and oxidative stress, evidence that neuroimmune activation drives alcohol-related neurotoxicity. As this study is currently available as a preprint, its findings should be interpreted with appropriate caution until peer review confirms their robustness.

Despite this compelling evidence from preclinical and post-mortem research, neuroimaging findings remain inconsistent. Studies using positron emission tomography (PET) with the microglial translocator protein (TSPO) radioligand N-(2-[^{11}C]methoxybenzyl)-2-phenoxy-5-pyridinamine ([^{11}C]PBR28) report inconsistent results, with lower or unchanged TSPO binding in detoxified SAUD patients [8–10]. This may reflect TSPO

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downregulation or microglial loss/dysfunction ("burn-out") after chronic activation, leading to impaired neuroprotection and cognitive deficits [8]. Conversely, acute alcohol exposure transiently increases TSPO binding in humans [11] and non-human primates [12], suggesting that neuroimmune responses to alcohol may be dynamic and time-sensitive and difficult to capture by single time-point scans. These findings underscore the need for longitudinal, multimodal designs that combine neuroimaging with peripheral biomarkers to track immune dynamics across intoxication and recovery [13].

To address this, we conducted a longitudinal, test-retest study in SAUD patients over three weeks of abstinence, designed to track within-subject changes in peripheral inflammation (via circulating cytokines), brain structure (via magnetic resonance imaging (MRI)), and clinical symptoms (depression, anxiety, craving, and alcohol withdrawal severity). This early abstinence window is characterized by rapid clinical improvement [14, 15] and partial normalization of peripheral cytokines [16], yet brain inflammatory processes in early abstinence are still poorly described [17], in part due to limitations in study design or timing. Recent MRI studies have shown evolving GM and white matter (WM) changes within the first weeks of abstinence [18, 19], changes that resemble microglial activation patterns observed in animal models [20]. However, direct evidence linking these changes to systemic inflammation or clinical outcomes in SAUD remains scarce.

We also focused on the ChP, increasingly recognized as key neuroimmune interfaces at the blood-cerebrospinal fluid (CSF) barrier [21]. The ChP act as immune sensors and modulators, and show structural and functional changes in other inflammatory disorders such as multiple sclerosis, Alzheimer, schizophrenia and major depression [21–24]. Despite their central immunological role, they remain unexplored in the context of SAUD.

We first expected to observe first signs of structural recovery in the brain over the three weeks detoxification, particularly in GM. Second, we hypothesized that there would be a partial resolution of systemic inflammation, reflected by a decrease in circulating pro-inflammatory cytokines. Since our analyses was limited to markers that would be systematically above the lower limit of detection in all participants, we did not make specific predictions about certain molecules. Third, we hypothesized that cerebral and immune changes would occur simultaneously over time, i.e., that the reduction in peripheral inflammation would correlate with volumetric normalization, particularly in the ChP, given their emerging role in neuroimmune signaling. Finally, we hypothesized that these biological changes would be related to clinical variables. However, due to the exploratory nature of the study, we did not make specific regional predictions, but rather adopted a global, whole-brain based approach.

To maximize interpretability, we tightly controlled the timing of MRI and cytokine assessments relative to last alcohol and food intake. This precise synchronization enabled us to better capture short-term neuroimmune dynamics and their potential role in early recovery from alcohol dependence.

METHODS

Participants

We recruited SAUD patients admitted to Saint-Luc Academic Hospital (Brussels, Belgium) for a three-week detoxification program from 2015–2019. Diagnosis was established by psychiatric interview (DSM-5), and patients had been drinking until the day of admission or the day before.

Exclusion criteria included chronic inflammatory bowel disease, rheumatoid arthritis or other chronic inflammatory conditions, cancer, obesity (Body Mass Index (BMI) > 30 kg/m^2), diabetes, and bariatric surgery. Patients were also excluded if they had taken antibiotics, probiotics, or prebiotics within two months, or anti-inflammatory drugs (NSAIDs/glucocorticoids) within one month before inclusion. Additional exclusions were cirrhosis, significant liver fibrosis (≥ F2 on Fibroscan), any other Axis I DSM-5 disorder or major cognitive impairment (i.e., a score of ≤25 on the Mini-Mental State Examination (MMSE); [25]), use of drugs other than alcohol/nicotine, or contraindications to MRI (pregnancy, pacemaker/metal implants, claustrophobia). All patients received diazepam (40–60 mg/day) at the start of detoxification, with progressive tapering.

A control group matched for age and sex was available for comparison of inflammatory markers and clinical symptoms. It was recruited via social-media advertisements. Volunteers received an information sheet and a prescreening questionnaire (demographics, alcohol use including Alcohol Use Disorders Identification Test (AUDIT) [26], brief medical/MRI-safety check). Inclusion criteria were age 18–65, low-risk alcohol use, AUDIT ≤ 7. Exclusion criteria were the same as for patients.

For patients, prior to consent, research staff assessed the capacity to understand study information, and their ability to express a choice voluntarily. Patients were informed that participation was voluntary, that they could withdraw at any time without consequence or impact on their treatment.

Procedure

Upon admission on Day 1, patients consenting to participate underwent an MRI scan (strictly between 6 and 8 h after admission for all patients) and received questionnaires to evaluate their clinical symptoms. Overnight fasting blood samples were taken from all participants on Day 2 between 8:00 and 8:30 AM. These tests together constituted the evaluation at time 1 (T1). At the end of the detoxification program (Day 19), patients were re-evaluated by MRI scanning, questionnaires for clinical symptoms, and blood sample, together constituting T2 (Fig. 1).

Given that early detoxification is a vulnerable period, special precautions were taken to ensure participant safety during MRI sessions. A trained medical technician and a member of the research team accompanied each patient to the scan, and participants were monitored throughout the session. A panic button was available, and patients were reminded that they could stop the scan at any time.

Clinical symptoms questionnaires

Symptoms of depression, anxiety, and alcohol craving were measured using three self-report questionnaires: the Beck Depression Inventory (BDI) [27], the State-Trait Anxiety Inventory (STAI Form YA) [28], and the Obsessive-Compulsive Drinking Scale (OCDS) [29]. The BDI, used in its French BDI-II version [30] comprises 21 items (maximum score 63; cutoffs: 0–11 minimal, 12–19 mild, 20–27 moderate, 28–63 severe) assessing depressive symptoms over the previous two weeks. The STAI Form YA's state subscale, which contains 20 items scoring current state anxiety (range 20–80; 20–39 low, 40–59 moderate, 60–80 high), was used in its validated French version [31]. The OCDS (14 items) captures cognitive aspects of craving in the preceding seven days; we employed a French translation [32], omitting items on current alcohol consumption, since participants were under supervised detoxification.

Withdrawal intensity scores were measured by nurses using the Cushman Scale [33], which evaluates heart rate, systolic blood pressure, respiration, tremor, perspiration, agitation, and sensory disturbances (each scored 0–3, total possible 18). These ratings were conducted three times on Day 2 at six-hour intervals, with averaging to give the overall withdrawal severity. Pre-hospitalization alcohol consumption (grams/day) over the previous 30 days was quantified using the timeline follow-back method [34].

Biological sample collection

Blood was collected in (ethylenediaminetetraacetic acid) EDTA tubes and centrifuged at 1000 g for 15 min at 4 °C. Plasma was stored at −80 °C until the time of analysis. Plasma levels of four inflammatory cytokines (Interleukin-8 (IL-8), monocyte chemoattractant protein-1 (CCL2) (MCP-1), macrophage inflammatory protein-1 beta (CCL4) (MIP-1β), and tumor necrosis factor-alpha (TNF-α)) were measured by a multiplex cytokine assay (Human Bio-Plex; Bio-Rad Laboratories Inc., Hercules, CA, USA) according to instructions from the manufacturer. These four cytokines were not selected a priori, but were the only analytes from the broader panel that consistently exceeded the lower limit of detection across participants. The choice thus reflects assay constraints rather than theory-driven selection. The detection thresholds were as follows: IL-8 (0.4 pg/mL), MCP-1 (1.9 pg/mL), MIP-1β (3.0 pg/mL), and TNF-α (0.7 pg/mL). Plasma levels of other kit analytes fell below their respective detection levels.

Fig. 1 Study protocol for alcohol detoxification and assessment. Timeline illustrating the study design across the three weeks of alcohol detoxification: T1 (Day 1/Day 2) at the start and T2 (Day 19) at discharge. Clinical evaluations, MRI imaging, and blood samples were collected at both time points to monitor changes in systemic inflammation, brain morphometry, and clinical symptoms.

MRI acquisition

Three-dimensional (3D) anatomical images with heavy T1-weighting were obtained using a 3 T Achieva scanner from Philips Healthcare, employing a 32-channel phased array head coil. Patients were instructed to stay still and were securely positioned in the head-holder coil, with the provision of soft earplugs for comfort. Motion was mitigated by stabilising the head and re-acquiring scans when motion was observed. The 3D sequence involved a gradient echo sequence with an inversion prepulse (Turbo Field Echo) captured in the sagittal plane, with parameters as follows: TR/TE/flip angle = 9.1 ms/4.6 ms/8°, 150 slices, slice thickness = 1 mm, FOV = 220 × 197 mm^2, acquisition matrix = 296 × 247 (refined to 320*320), in-plane resolution = 0.81 × 0.95 mm^2 (acquisition) refined to 0.75 × 0.75 mm^2, and a SENSE factor = 1.5 (for parallel imaging).

The whole brain was analyzed and volumetrically segmented in the FreeSurfer image analysis suite (version 6) (http://surfer.nmr.mgh.harvard.edu/), using a series of automated steps. This final volumetric segmentation amalgamates data derived from a universal probabilistic atlas and subject-specific measured values, allowing for detailed volumetric analysis. The reference atlas derives from a training set of 40 healthy young subjects, whose brain structures were manually labeled [35–37].

T1-weighted images underwent rigorous visual quality control. Scans showing visible motion artefacts or failed segmentation were excluded, minor skull-stripping inaccuracies were corrected before volumetry.

Statistical analyses

We enrolled all eligible SAUD patients during the recruitment period (n = 37), a sample size comparable to prior studies (n ≈ 25–40) that detected significant MRI and cytokine changes in early abstinence [16, 38–40]. Between-group (T1 vs. controls) comparisons of demographics, clinical scores and cytokines used two-sided t-tests (Levene's/Welch's or nonparametric as needed), and within-patient T1-T2 changes employed paired t- or Wilcoxon tests. Change was defined as a difference score (T2 minus T1). This matches our within-subject test-retest design and avoids collinearity that can arise when controlling baseline in small samples [41]. Correlations (Pearson or Spearman, according to normality) were analyzed. For cytokines, distributions were skewed, accordingly, we reported medians and interquartile ranges [IQR] and used non-parametric tests (Wilcoxon/Spearman) rather than log-transformations. Results were corrected at 5% false discovery rate (FDR), with uncorrected p-values reported to highlight trends for future, larger cohorts. MRI volumes were investigated atlas-wide using FreeSurfer's ASEG (cortical and WM macro-structures, subcortical nuclei, ventricles and ChP, corpus callosum) and Desikan-Killiany lobar parcellations (left/right combined). FDR was applied within each anatomical group, Cohen's d quantified effect sizes, and for nonsignificant effects we calculated the N required for 80% power. These values are provided in the Supplementary Material. Because the MRI analyses were within-subject, participants served as their own controls and therefore neither age nor sex was included as a covariate in the primary MRI models. Smoking was highly homogeneous (most patients were daily smokers at both time points) and was not modelled. In exploratory analyses, we tested whether sex, age, or baseline daily alcohol were associated with change scores (T2-T1) using two-sample t-tests (Mann-Whitney U when non-normal) and Pearson/Spearman correlations, as appropriate. All analyses were performed in R 4.2.2.

RESULTS

Participants

The final sample of SAUD patients were 21 males and 16 females with a mean age of 46 years. Most patients (35/37) were smokers. The median alcohol consumption was 101 units (IQR = 106) of alcohol (10 g) per week. Women (M = 84, SD = 48) drank less alcohol than men (M = 143, SD = 95) before entering detoxification ($t(31) = 2.116$, $p = 0.042$). The control group included ten women and seven men with a mean age of 43 years, only one of whom was a smoker. The two groups did not differ in age ($p = 0.450$), or sex ($\chi^2 = 0.5945$, $p = 0.440$). However, the control group differed significantly from the SAUD group (at T1) in terms of lower scores for depression (Wilcoxon $W = 451$, $p < 0.001$), anxiety (Wilcoxon $W = 410$, $p = 0.003$), and craving measures (Wilcoxon $W = 515$, $p < 0.001$). See Table 1.

Clinical data and evolution with alcohol cessation

In the SAUD group, all clinical symptoms decreased from T1 to T2. Depression scores transitioned from moderate to minimal levels (Wilcoxon $W = 411$, $z = -4.19$, $p < 0.001$). State anxiety scores decreased from moderate to low levels (Wilcoxon $W = 343$, $z = -2.27$, $p = 0.023$). Total craving score also showed a statistically significant reduction ($t(28) = 5.921$, $p < 0.001$). See Table 1.

Inflammation levels and evolution with alcohol cessation

We first examined whether SAUD patients differed from controls at the two different time points (T1 and T2) with respect to the four plasma inflammation markers IL-8, MCP-1, MIP-1β, and TNF-α. The T1 and T2 levels in patients were both compared to the single measurements in the control group.

All four cytokines were significantly higher at T1 (MCP-1: $z = 0.014$, $p = 0.014$, FDR-corrected $p = 0.014$, TNF-α: $t(47) = 2.77$,

Table 1. Demographic and clinical data of the patients (SAUD, N = 37) (T1 and T2) and the controls (CTRL, N = 17).

Variable		Group	Mean (SD)	Median(IQR)	Min-Max	P value
Age (Years)		**SAUD**	46.11 (± 11.04)	46 (15)	29–71	p = 0.450
		CTRL	43.12 (± 8.31)	41 (15)	30–55	
Sex		**SAUD**	21 men (56.8%)	16 women (43.2%)	-	p = 0.440
		CTRL	7 men (41.2%)	10 women (58.8%)	-	
Smokers		**SAUD**	2 non-smokers (5.4%)	35 smokers (94.6%)	-	p < 0.001
		CTRL	16 non-smokers (94.1%)	1 smoker (5.9%)	-	
Alcohol units/ week*		**SAUD**	118.44 (± 82.80)	100.8 (105.9)	24–350	-
Withdrawal symptoms (Cushman)		**SAUD**	7.03 (± 5.29)	6 (6.5)	0–21	-
Depressive symptoms (BDI)						
	T1	**SAUD**	24.13 (± 10.99)	24.5 (15.75)	3–48	p < 0.001
		CTRL	8.18 (± 7.69)	5 (11)	1–25	
	T2	**SAUD**	14.09 (± 11.96)	10 (15)	0–43	-
Anxiety symptoms (STAI)						
	T1	**SAUD**	43.88 (± 10.26)	44.5 (15.25)	276–2	p = 0.003
		CTRL	34.18 (± 10.18)	33 (15)	22–58	
	T2	**SAUD**	38.70 (± 13.52)	38 (25)	20–64	-
Craving (OCDS)						
	T1	**SAUD**	15.42 (± 6.53)	16 (7)	0–28	p < 0.001
		CTRL	1.06 (± 1.60)	0 (2)	0–5	
	T2	**SAUD**	9.24 (± 6.14)	9 (8)	0–20	-

*1 unit is 10 grams of pure alcohol.
Sex and Smoker are categorical; no mean/median applies.
BDI beck depression inventory.
STAI state-trait anxiety inventory (State subscale).
OCDS obsessive-compulsive drinking scale.
A Wilcoxon test was used for BDI, STAI-State, and OCDS. For Age, a Welch's *t*-test was performed.
SAUD severe alcohol use disorder group, *CTRL* control group.
("-") indicate no formal test or not applicable data.

p = 0.008, FDR-corrected p = 0.014, MIP-1β: z = 4.45, p < 0.001, FDR-corrected p < 0.001, IL-8: z = 2.43, p = 0.014, FDR-corrected p = 0.014) in SAUD than control subjects. At T2, TNF-α (z = 2.75, p = 0.006, FDR-corrected p = 0.012), and MIP-1β (t(49) = 4.25, p < 0.001, FDR-corrected p < 0.001) levels remained higher in patients compared to control data.

We next examined the evolution of each cytokine over time in SAUD patients. There was a statistically significant decrease in the plasma levels of MCP-1 (z = 2.04, p = 0.041, FDR-corrected p = 0.056), MIP-1β (z = 2.51, p = 0.012, FDR-corrected p = 0.036), and IL-8 (z = −0.29, p = 0.018, FDR-corrected p = 0.036), between T1 and T2. No such trend was observed for TNF-α, as its levels increased in half of the patients (N = 15) and decreased in the other half (N = 16). Given the high variability of MCP-1 levels in the population, we calculated the 95% confidence interval for their median difference 3.87–36.80 pg/ml. Notably, the lower end of this interval exceeds zero, thus reinforcing our finding of a significant reduction in MCP-1 levels between T1 and T2. See Fig. 2.

Early changes in brain volume with alcohol cessation

We observed a significant rise from T1 to T2 in GM volume in both cortical (t(36) = 2.651, p = 0.012, FDR p = 0.020) and subcortical (t(36) = 3.343, p = 0.002, FDR p = 0.007) components, as well as in cerebellar GM (t(36) = 3.245, p = 0.003, FDR p = 0.007). WM volumes did not change significantly, except for an increase in cerebellar WM (t(36) = 2.399, p = 0.022, FDR p = 0.027).

We also noted significant volumetric decreases for the ChP (t(35) = 2.097, p = 0.043, FDR p = 0.048) and the third (t(35) = 2.093, p =0.044, FDR p = 0.048), fourth (t(35) = 3.674, p <0.001), and lateral ventricles (t(35) = 2.049, p =0.048, FDR p = 0.048). No significant changes were observed in any of the corpus callosum subdivisions.

Examining specific subcortical Region of interest (ROIs) revealed volumetric increases in the thalamus (t(36) = 2.342, p = 0.025) and ventral diencephalon (t(36) = 2.071, p = 0.046), though neither survived FDR correction (Supplementary Table 1).

Using the Desikan-Killiany "aparc" atlas to analyze cortical GM first by lobe, we found significant global volumetric increases for the frontal (t(36) = 2.414, p = 0.021, FDR p = 0.043), parietal (t(36) = 2.321, p = 0.026, FDR p = 0.043), and occipital lobes (t(36) = 2.928, p = 0.006, FDR p = 0.030). There were subregional volumetric increases surviving FDR correction for multiple comparisons in the frontal pole (t(36) = 2.829, p = 0.008, FDR p = 0.044), caudal middle frontal gyrus (t(36) = 2.920, p = 0.006, FDR p = 0.044), pericalcarine cortex (t(36) = 2.581, p = 0.014, FDR

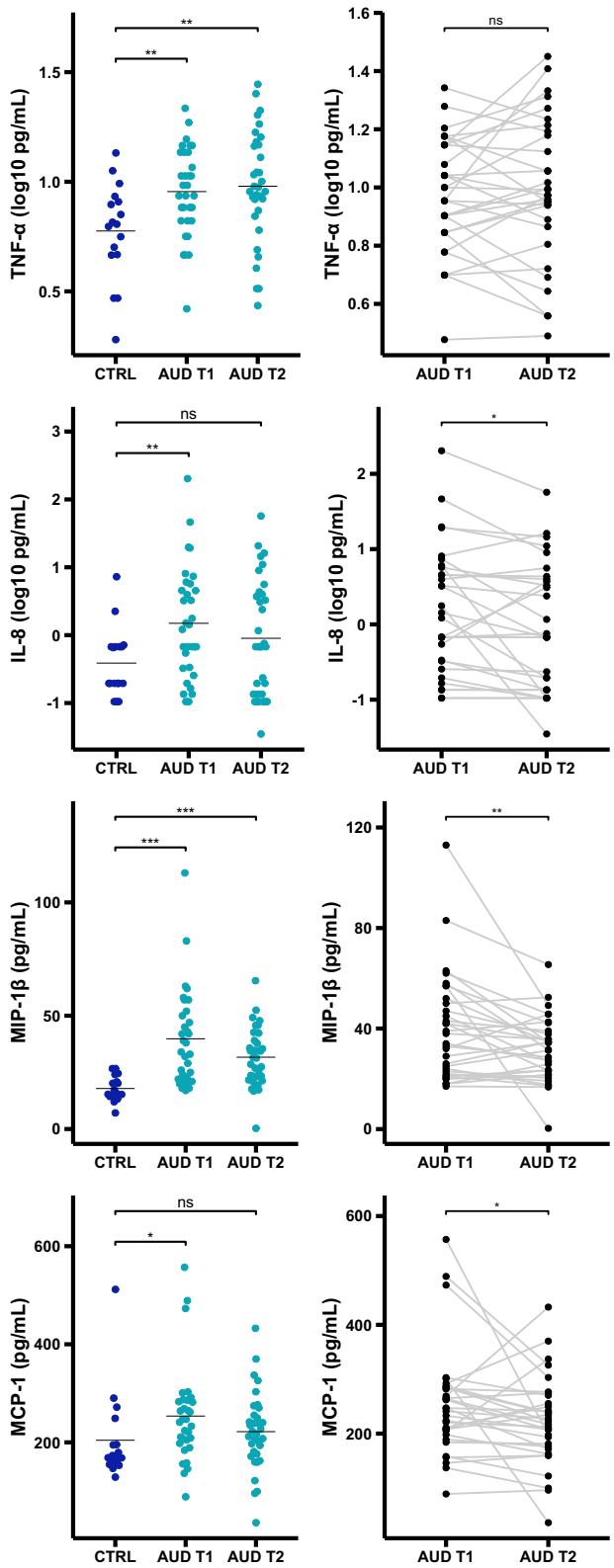

Fig. 2 Circulating cytokine levels in SAUD patients and controls. Plasma concentrations of cytokines in patients at T1 and T2 compared to controls. TNF-α and IL-8 values were log10-transformed for visualization. Data are shown as individual values with mean ± crossbar. Statistical comparisons are indicated by brackets (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ns, not significant).

$p = 0.018$), cuneus ($t(36) = 2.693$, $p = 0.011$, FDR $p = 0.018$), and lateral occipital cortex ($t(36) = 2.988$, $p = 0.005$, FDR $p = 0.018$). (Supplementary Table 2).

Links between changes in the ventricles and changes in other structures

Next, we tested whether ventricular volume reductions between T1 and T2 correlated with significant increases observed in other brain structures in the FreeSurfer automated subcortical segmentation (ASEG) atlas (cortical GM, subcortical GM, cerebellar GM and WM, the thalamus, the ventral diencephalon, and the ChP). To capture overall ventricular shrinkage, we computed a composite score summarizing volume changes across the third, fourth, and lateral ventricles. We found statistically significant negative correlations between changes in ventricle volume and subcortical GM ($r = -0.448$, $p = 0.005$, FDR $p = 0.018$). Associations with cerebellar GM ($r = -0.419$, $p = 0.010$, FDR $p = 0.103$), and cerebellar WM ($\rho = -0.364$, $p = 0.027$, FDR $p = 0.103$) were also found but without surviving FDR. Among subcortical regions, the thalamus showed a negative correlation with ventricle volume ($r = -0.642$, $p < 0.001$, FDR $p < 0.001$). In contrast, no significant correlations were found between changes in ChP volume and ventricular structures.

Modulatory effect of demographic variables on morphometric changes and inflammation levels

Additional analyses explored potential demographic influences on brain volume and cytokine changes from T1 to T2. Significant sex effects emerged for total and GM volume increases, notably in subcortical, cerebellar, occipital, and frontal regions (p-values ranging from 0.015–0.048), although these did not withstand FDR correction. Further paired t-tests revealed volume changes to be significant only in the men. There was no significant sex-based differences in cytokine concentrations. Additionally, neither age nor daily alcohol consumption correlated with volumetric or cytokine changes, and the high prevalence of smokers in the sample (35 out of 37) precluded analysis of smoking's impact.

Associations between brain volume changes and changes in clinical symptoms

To investigate possible relationships between changes in clinical symptoms and brain volume from T1 to T2, we examined overall regions (main GM divisions) and then explored each cortical and subcortical subregion in more detail. No significant correlations emerged for anxiety, depression, or withdrawal severity. By contrast, changes in craving showed a negative association with changes in cortical GM volume ($r = -0.386$, uncorrected $p = 0.042$, FDR > 0.05). An exploratory, uncorrected survey across cortical regions revealed negative correlations in several frontal regions (caudal middle frontal gyrus: $r = -0.41$, $p = 0.028$; paracentral lobule: $r = -0.40$, $p = 0.033$; precentral region: $r = -0.39$, $p = 0.039$), the temporal lobe (inferior temporal cortex: $r = -0.38$, $p = 0.046$; banks of the superior temporal sulcus: $r = -0.42$, $p = 0.025$), and the parietal lobe (inferior parietal cortex: $r = -0.39$, $p = 0.041$; supramarginal gyrus: $r = -0.47$, $p = 0.011$; precuneus: $r = -0.52$, $p = 0.004$). Additionally, the volume of the posterior corpus callosum correlated negatively with changes in craving ($r = -0.494$, $p = 0.008$). Overall, these findings indicate that individuals who showed larger volume increases in these specific regions also experienced greater reductions in craving.

Associations between brain volume changes and inflammatory changes

To examine a potential link between inflammation and ChP volume, we tested cytokine-ChP associations at both time points

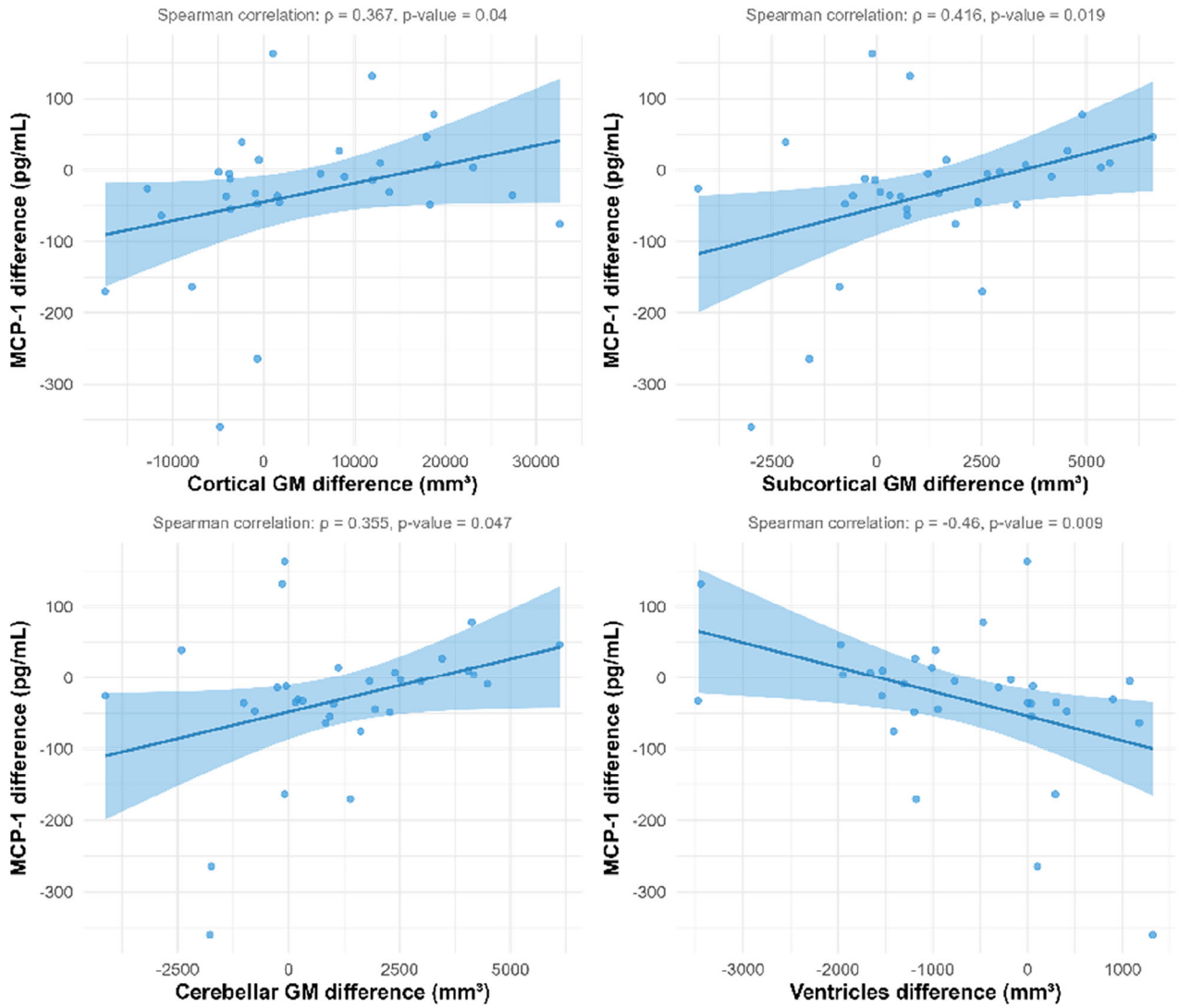

Fig. 3 Associations between changes in MCP-1 concentration from T1 to T2 and changes in brain tissue compartment volumes during early abstinence. Scatterplots show the associations for cortical grey matter (top left), subcortical grey matter (top right), cerebellar grey matter (bottom left), and ventricular volume (bottom right). Points represent individual participants. Spearman correlation coefficients (ρ) and corresponding p-values are reported in each panel. The solid line represents the fitted regression line and shaded areas indicate the 95% confidence interval.

and then explored whether changes in cytokines between T1 and T2 predicted changes in ChP volume. Positive correlations emerged at T1 between ChP volume and both MCP-1 ($\rho = 0.364$, $p = 0.040$, FDR $p = 0.080$) and MIP-1β ($\rho = 0.378$, $p = 0.033$, FDR $p = 0.080$), indicating a trend toward significance after FDR correction.

We then evaluated whether shifts in cytokines from T1 to T2 related to significant regional volume changes. In this exploration, MCP-1 stood out, displaying a significant positive correlation with cortical ($\rho = 0.367$, $p = 0.040$, FDR $p = 0.094$), subcortical ($\rho = 0.416$, $p = 0.019$, FDR $p = 0.076$), and cerebellar GM volumes ($\rho = 0.355$, $p = 0.047$, FDR $p = 0.094$), and a significant negative correlation with ventricular volume ($\rho = -0.460$, $p = 0.009$, FDR $p = 0.072$). Within the cortex, the temporal lobe showed the strongest association ($\rho = 0.562$, $p < 0.001$, FDR $p = 0.003$): declining MCP-1 coincided with shrinking GM volumes and ventricle enlargement (see Fig. 3).

We next made an exploratory investigation of all cortical subregions by lobe that correlated positively with the individual changes in MCP1 concentration. In the temporal lobe, there were correlations in the fusiform gyrus ($\rho = 0.367$, $p = 0.039$), inferior temporal gyrus ($\rho = 0.406$, $p = 0.022$), middle temporal gyrus ($\rho = 0.387$, $p = 0.028$) and superior temporal gyrus ($\rho = 0.427$, $p = 0.015$). In the frontal lobe, correlations were confined to parts of the inferior frontal gyrus: the pars orbitalis ($\rho = 0.383$, $p = 0.031$), the pars opercularis ($\rho = 0.399$, $p = 0.024$), and the pars triangularis ($\rho = 0.462$, $p = 0.008$) and in the medial orbitofrontal cortex ($\rho = 0.564$, $p = 0.001$). In addition, the cingulate isthmus ($\rho = 0.365$, $p = 0.040$) also showed a significant correlation. Among subcortical regions, only the volume change in thalamus correlated with the decrease in plasma MCP -1 ($\rho = 0.364$, $p = 0.040$). Moreover, the insula also exhibited a significant positive correlation with the MCP-1 reduction ($\rho = 0.361$, $p = 0.042$).

Associations between inflammatory changes and changes in clinical symptoms

We found no link between cytokine levels and changes from T1 to T2 in depression, anxiety, or craving symptoms in the SAUD patients, nor were there any such associations in the control

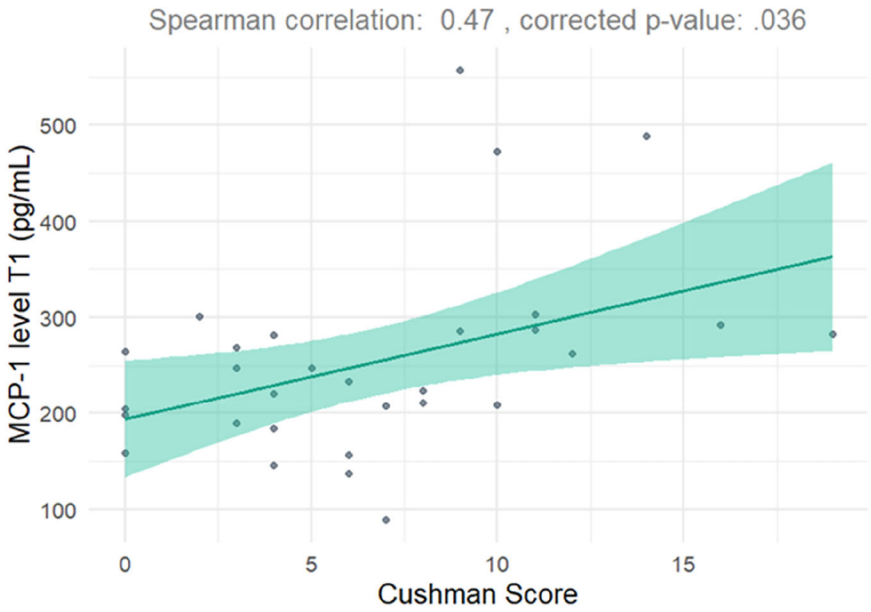

Fig. 4 Association between baseline MCP-1 concentration and withdrawal severity at T1. Scatterplot showing the association between Cushman score and MCP-1 concentration at T1. Points represent individual participants. The solid line represents the fitted regression line and shaded areas indicate the 95% confidence interval.

group. However, the SAUD patients showed a statistically significant, positive correlation between the Cushman withdrawal score and MCP-1 level at T1 ($\rho = 0.469$, uncorrected $p = 0.009$, FDR-corrected $p = 0.036$). See Fig. 4.

DISCUSSION

Clinical changes during detoxification

Results confirmed a positive trajectory in the psychological well-being of SAUD patients across the detoxification process, with significant reductions in the levels of anxiety, depression and craving in the first three weeks of supervised detoxification, aligning with previous findings [14, 15, 42].

Cytokine dynamics and link with withdrawal symptoms

At the onset of detoxification, patients exhibited elevated plasma levels of all four cytokines, reflecting a low-grade systemic pro-inflammatory state [16, 40, 43]. A key new observation is that baseline MCP-1 correlated with withdrawal severity, and not total alcohol intake, pointing to a specific link between inflammation and symptom intensity. MCP-1 drives monocyte recruitment, microglial activation, and increased BBB permeability [44] which may amplify systemic and central immune responses during abrupt cessation. In animal models, MCP-1 spikes by up to 1000% within 18 h of ethanol withdrawal, coinciding with falling blood alcohol levels and supporting the concept of a withdrawal-specific neuroimmune rebound [45, 46].

Over 19 days of supervised detoxification, MCP-1 and IL-8 declined toward control levels [40, 47], MIP-1β also decreased but remained higher than controls, and TNF-α showed no net change (it rose in roughly half the patients and fell in the other half), in line with prior observations [16, 48]. Longer follow-up may be required for stable declines in some cytokines such as TNF-α [40] and inter-individual variability may reflect genetic or lifestyle factors [49]. Consistent with a recent review [43], these heterogeneous normalization rates likely reflect rapid improvement in gut permeability/endotoxemia during abstinence, which can dampen chemokine release [50, 51] and persistent peripheral drivers and longer-lived immune adaptations (e.g., smoking) sustaining MIP-1β or TNF-α [52].

Link between cytokines and the choroid plexus

MCP-1 and MIP-1β levels positively correlated with ChP volume at T1. The ChP, principal producer of CSF, acts as an immune gateway, coordinating leukocyte entry and cytokine exchange between blood and CSF [53, 54]. Its enlargement is a recognized marker of neuroinflammation across psychiatric disorders and likely reflects leukocyte infiltration, oedema, and cytokine-driven epithelial proliferation/remodeling [21]. MCP-1 and MIP-1β, as key chemokines for monocyte recruitment [55], may exert a specific influence on ChP structure. Our data provide the first evidence of a ChP-cytokine link in SAUD and, with the subsequent ChP shrinkage observed at T2, these results suggest that the ChP may act as a dynamic interface of resolution of neuroimmune alterations during early abstinence. Of course, validation in larger, independent cohorts is needed before establishing its role as a biomarker.

Substance use may accelerate brain aging, as shown in methamphetamine use disorder with older-appearing brains, atrophy, and ChP abnormalities during early abstinence [56]. In alcohol use disorder, we similarly observed early gray-matter recovery, ventricular-parenchymal coupling, and ChP changes linked to MCP-1, in line with prior reports of accelerated aging signatures [57]. Given evidence that ChP morphology predicts cognitive risk in aging, future work should test whether ChP volume and brain-age indices in alcohol use disorder predict cognition, treatment response, and relapse [58].

Structural brain changes during detoxification

No significant overall WM evolution. Apart from the cerebellum, we found no significant WM changes across detoxification, suggesting that substantial axon remodelling or remyelination does not occur within two to three weeks of abstinence. This aligns with an earlier study showing limited WM recovery at two weeks [39], but may differ from microstructural findings that revealed subtler early changes [18, 19, 59]. Such discrepancies may reflect the limitations of T1-based volumetry in detecting localized tract-specific remodeling, which might require longer sobriety or more sensitive imaging modalities. Notably, the cerebellum GM volume appeared to recover more rapidly, implying distinct regional plasticity in early abstinence [39].

Two coexisting patterns in brain changes

Our results suggest two coexisting trends in the evolution of brain recovery during abstinence.

Recovery-dominated pattern

On the one hand, the group-level analysis revealed a general recovery dynamic associated with alcohol cessation, marked by an overall increase in GM volume. The increase in cerebral cortex was driven by specific regions (middle and superior frontal areas, associative parietal areas, and most of the occipital lobe), and the subcortical increase was driven by the diencephalon and the thalamus, with an additional component from the cerebellum. Previous studies have already noted widespread GM recovery within two weeks of abstinence [17, 38, 39, 60–62], although the baseline intervals for those cohorts varied, which complicates a direct comparison with present results following a more tightly controlled timeline. The observed GM volume increases may reflect a combination of biological mechanisms associated with early abstinence, including tissue rehydration [63–65], improved cerebral perfusion [66–68], dendritic regrowth [63, 69], and possibly neurotransmitter rebalancing [70–72]. While the first two are primarily physiological processes rather than markers of structural restoration per se, they may contribute to macroscopic volume changes detected via MRI. Likewise, neurotransmitter rebalancing, although not directly volumetric, may promote synaptic remodeling or glial support processes that contribute to overall tissue integrity and subtle structural recovery [73]. Concurrent reductions in ventricular volume, likely a direct effect of expansion of the surrounding GM [62, 74], indeed correlated with the GM gains which mirrored previous findings at two [39] to four weeks [75] post- detoxification. The GM increase also correlated with the decrease in craving in our SAUD patients, suggesting a possible clinical importance of these changes. Volume increase in frontal subregions (caudal middle frontal, paracentral lobule, and precentral gyrus) is expected to reinforce executive inhibition and motor suppression of alcohol-seeking behavior [1]. Temporal lobe structures (inferior temporal cortex, superior temporal sulcus) facilitate visual association and socio-emotional processing [76], recovery of which might dampen cue-reactivity [1]. Gains in parietal areas (inferior parietal cortex, supramarginal gyrus, precuneus) mediate attentional bias, multi-sensory integration, and self-referential cognition [77], which might also mediate aspects of recovery. Finally, expansion of the posterior corpus callosum likely enhances inter-hemispheric signaling, thereby improving top-down regulatory control over reward circuits [78].

While GM increase paralleled the decline in craving, the temporal profile of MCP-1 did not, (consistent with [43]) suggesting that clinical improvement aligns more with structural restoration than with chemokine normalization, a dissociation future multimodal studies should probe explicitly.

Inflammation-resolution pattern

In addition, individual-level correlations between regional brain volume decreases and MCP-1 reduction in specific regions (inferior frontal areas, temporal lobe structures, the insula, and the cingulate isthmus) suggest a second mechanism, possibly reflecting the resolution of inflammation.

In the early stages of abstinence, elevated MCP-1 may contribute to microglial activation and BBB dysfunction. Although fully phagocytic amoeboid microglia are not typically observed in SAUD [79], studies report a partially activated, pro-inflammatory microglial state whether driven by chronic alcohol exposure [5, 80] or by a rebound effect during detoxification [81, 82]. This phenotype is sufficient to trigger cytokine release, astrocyte activation and increased BBB permeability [83]. MCP-1 itself has been shown to directly increase BBB permeability [44], while astrocytic aquaporins facilitate vasogenic oedema [84], transiently expanding regional volume. Diffusion-MRI and histology further show that microglial soma hypertrophy and process retraction enlarge the extracellular space and can raise regional volume even without cell-number changes [82, 85]. As inflammation resolves, microglia revert to a ramified state [86] and barrier integrity is restored, possibly producing the GM contraction found here to be associated with the decrease in MCP-1. In our sample, this process unfold within two weeks, consistent with the known rapid dynamic of microglial (partial) deactivation [82, 87, 88] and the normalization of lipopolysaccharide (LPS) and MCP-1 early in abstinence [16]. Participants with the greatest GM deflation showed lesser shrinkage or paradoxical enlargement of ventricles, consistent with Monro-Kellie principle which states that as intracranial volume is constant, the reductions in brain tissue are compensated by relative expansions in cerebrospinal fluid or blood volume [89]. Although MCP-1 was not measured in brain tissue directly, its correlations with structural changes, ChP volume, and withdrawal severity supports a model in which peripheral immune signaling, via BBB or ChP pathways, contributes to transient neuroinflammatory brain remodeling during early abstinence. The affected regions are known to host microglia with high activation potential [90] and are particularly vulnerable to inflammation across psychiatric disorders [91, 92]. Within this network, the insula is a key hub: it integrates interoceptive and affective signals [93], responds to peripheral immune challenges [94] and has been consistently implicated in craving and relapse risk in alcohol use disorder [95, 96].

Co-existent patterns of response (post-alcohol recovery and inflammation resolution) may cancel out at the group level, such that some structural changes did not emerge as significant in the T1-T2 comparison. However, we see in our population a clustering of responses (see Fig. 5): “recovery-dominant” regions showing an overall volume increase independent of MCP-1 decline; (2) “inflammation-modulated” regions with no significant volume change, but strong correlations to MCP-1 reduction; and (3) “mixed-effect” areas (thalamus, cerebellum, pars opercularis) that may exhibit a volume gain along with a “microglial deflation” component, thus tempering the net volumetric increase at T2.

By demonstrating tight co-modulation of peripheral chemokines, ChP dynamics and regional GM volumes, our study reinforces the need for integrated neuro-immune models of SAUD. The observed MCP-1-ChP association is preliminary but highlights a pathway that deserves replication in larger samples before being considered a biomarker or therapeutic target.

Sex and SAUD severity effects

Sex-related volume brain volume changes, aligned with known sex differences in alcohol metabolism, toxicity, and immunity [97, 98], lost significance after FDR correction, indicating limited power. Age and pre-detoxification alcohol intake were not associated with brain or cytokine measures, suggesting that abrupt cessation, rather than cumulative exposure, drives neuro-immune observations.

Study limitations and future directions

A first limitation is the potential influence of smoking. Nearly all patients were daily smokers, which prevented modeling smoking as a covariate but also reflects the clinical reality of alcohol use disorder (typically 60–90% in the literature) [99]. Smoking exerts both chronic pro-inflammatory effects [100] and transient immunosuppressive effects of nicotine [101] and has been associated with cortical thinning and accelerated brain aging [102, 103]. It may therefore have contributed to elevated cytokines at baseline, while its continuation would be expected to maintain inflammation, blunt recovery, and diminish the extent of cerebral structural restoration, making our findings likely conservative. However, detailed measures such as pack-years were not collected. Likewise, all patients had received only a single 10 mg

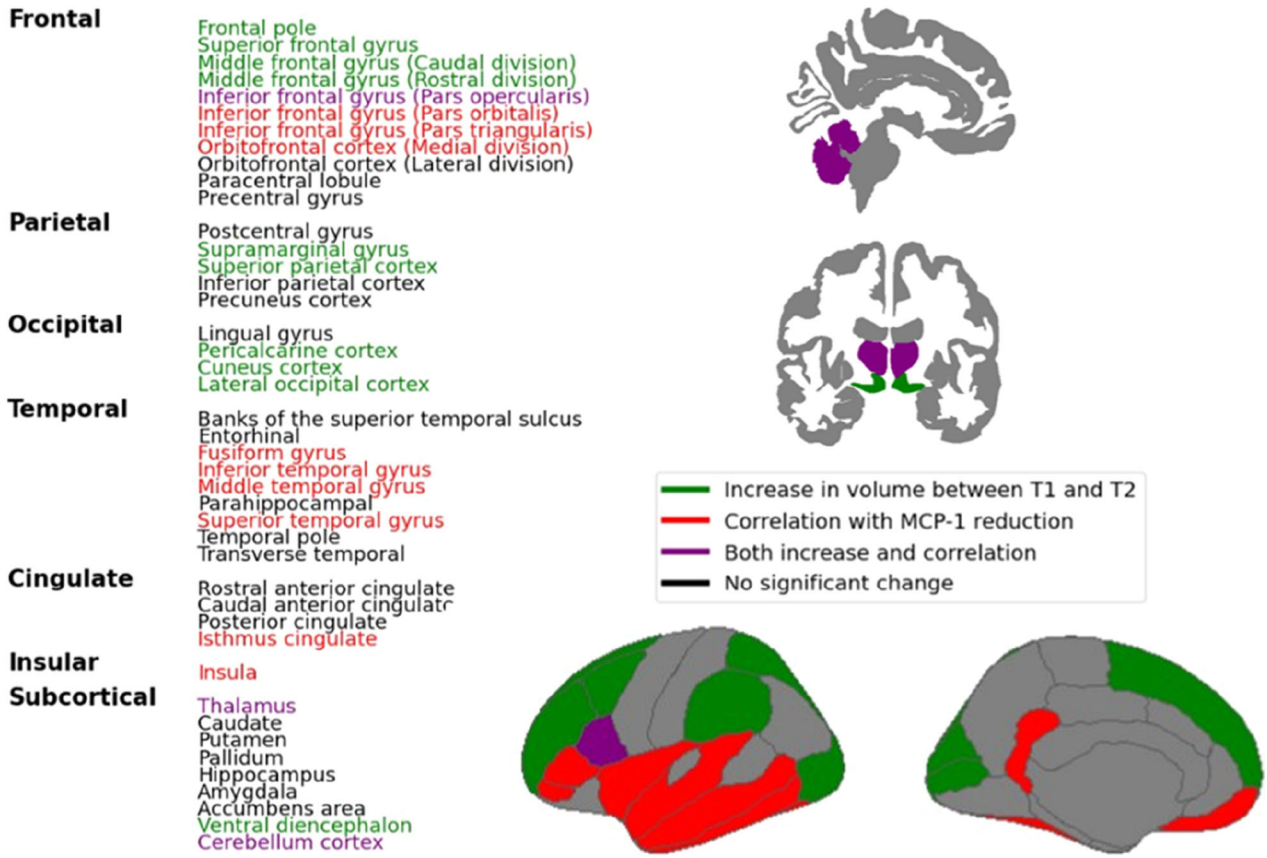

Fig. 5 Color-coded map of cortical and subcortical regions, illustrating different patterns of volumetric change after three weeks of abstinence in SAUD patients. Green indicates a significant volume increase between T1 and T2. Red denotes regions in which volume change correlated with declining plasma MCP-1 level. Purple highlights areas that show regions with concomitant group-level volume increase and a correlation with MCP-1 decline. Black marks regions with no significant change.

dose of diazepam at the time of the first MRI, and the medication had been fully tapered by the second MRI. Benzodiazepines can dampen immune responses [104, 105] and may influence brain structure [106]. However, given its short-term and low-dose use, a major impact is unlikely. The robust cytokine elevations and brain-immune associations observed suggest that inflammation was strong enough to be captured despite these potential confounders. More broadly, unmeasured factors such as such as BMI, lifestyle (diet, activity, sleep), genetics, and sociodemographic variables (marital status, education, employment) may also shape recovery and should be included in future studies to better explain variability and improve generalizability [49, 107–109]. A key strength lies is our precise control of the timing of alcohol cessation relative to measurements: all participants drank until admission or the day before, but we lacked exact final drinking episode, drinking-day averages, and age-at-first-drink data, which could moderate outcomes. A minority (N = 10) showed paradoxical anxiety increases, suggesting individual trajectories that merit targeted follow-up. Finally, only four cytokines exceeded the assay's detection threshold across participants and thus entered analyses, limiting biomarker coverage. Although MCP-1 was the strongest signal, other immune molecules may be equally relevant. Notably, IL-6, often elevated in SAUD meta-analyses [43] fell below threshold in our cohort. More refined kits or high sensitivity assays should be used in future studies to better capture low grade inflammatory states that is usually observed in SAUD patients and to expand the coverage of both pro, and anti-inflammatory pathways involved in alcohol withdrawal and recovery.

We applied an atlas-wide, FDR-corrected analysis to keep false positives low, but we also show uncorrected trends to show effects that need larger samples. Because strict correction in a single cohort can hide biologically relevant signals [110, 111], replication in an independent sample is essential, an approach now widely recommended for exploratory neuroimaging [112, 113].

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding authors upon written request.

REFERENCES

1. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016;3:760–73.
2. Erickson EK, Grantham EK, Warden AS, Harris RA. Neuroimmune signaling in alcohol use disorder. Pharmacology Biochem Behav. 2019;177:34–60.
3. Ahlers KE, Karaçay B, Fuller L, Bonthius DJ, Dailey ME. Transient activation of microglia following acute alcohol exposure in developing mouse neocortex is primarily driven by BAX-dependent neurodegeneration: microglia and developmental alcohol exposure. Glia. 2015;63:1694–713.
4. Holloway KN, Douglas JC, Rafferty TM, Kane CJM, Drew PD. Ethanol induces neuroinflammation in a chronic plus binge mouse model of alcohol use disorder via TLR4 and MyD88-Dependent Signaling. Cells janv. 2023;12:2109.
5. Crews FT, Qin L, Coleman L, Vidrascu E, Vetreno R. Cortical reactive microglia activate astrocytes, increasing neurodegeneration in human alcohol use disorder. Brain Behav Immun. 2026;131:106156
6. De Carvalho LM, Wiers CE, Sun H, Wang GJ, Volkow ND. Increased transcription of TSPO, HDAC2, and HDAC6 in the amygdala of males with alcohol use disorder. Brain Behav. 2021;11:e01961.

7. Vetreno RP, Qin L, Coleman JrLG, Crews FT. Increased Toll-like Receptor-MyD88-NFκB-Proinflammatory neuroimmune signaling in the orbitofrontal cortex of humans with alcohol use disorder. Alcoholism: Clin Exp Res. 2021;45:1747–61.
8. Hillmer AT, Sandiego CM, Hannestad J, Angarita GA, Kumar A, McGovern EM, et al. In vivo imaging of translocator protein, a marker of activated microglia, in alcohol dependence. Mol Psychiatry. 2017;22:1759–66.
9. Kalk NJ, Guo Q, Owen D, Cherian R, Erritzoe D, Gilmour A, et al. Decreased hippocampal translocator protein (18 kDa) expression in alcohol dependence: a [^{11}C]PBR28 PET study. Transl Psychiatry. 2017;7:e996.
10. Kim SW, Wiers CE, Tyler R, Shokri-Kojori E, Jang YJ, Zehra A, et al. Influence of alcoholism and cholesterol on TSPO binding in brain: PET [11 C]PBR28 studies in humans and rodents. Neuropsychopharmacology août. 2018;43:1832.
11. Raval NR, Angarita G, Matuskey D, Miller R, Drake LR, Kapinos M, et al. Imaging the brain's immune response to alcohol with [11C]PBR28 TSPO Positron Emission Tomography. Mol Psychiatry. 2023;2:1–7.
12. Saba W, Goutal S, Auvity S, Kuhnast B, Coulon C, Kouyoumdjian V, et al. Imaging the neuroimmune response to alcohol exposure in adolescent baboons: a TSPO PET study using 18F-DPA-714. Addiction Biol. 2018;23:1000–9.
13. Li X, Ramos-Rolón AP, Kass G, Pereira-Rufino LS, Shifman N, Shi Z, et al. Imaging neuroinflammation in individuals with substance use disorders. J Clin invest. 2024;134:e172884.
14. de Timary P, Cordovil de Sousa Uva M, Denoël C, Hebborn L, Derely M, Desseilles M, et al. The associations between self-consciousness, depressive state and craving to drink among alcohol dependent patients undergoing protracted withdrawal. PLoS ONE. 2013;8:e71560.
15. Petit G, Luminet O, Cordovil de Sousa Uva M, Monhonval P, Leclercq S, Spilliaert Q, et al. Gender differences in affects and craving in alcohol-dependence: a study during alcohol detoxification. Alcohol Clin Exp Res. 2017;41:421–31.
16. Leclercq S, Cani PD, Neyrinck AM, Stärkel P, Jamar F, Mikolajczak M, et al. Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects. Brain, behavior, Immun. 2012;26:911–8.
17. Parvaz MA, Rabin RA, Adams F, Goldstein RZ. Structural and functional brain recovery in individuals with substance use disorders during abstinence: a review of longitudinal neuroimaging studies. Drug Alcohol Dependence. 2022;232:109319.
18. De Santis S, Bach P, Pérez-Cervera L, Cosa-Linan A, Weil G, Vollstädt-Klein S, et al. Microstructural white matter alterations in men with alcohol use disorder and rats with excessive alcohol consumption during early abstinence. JAMA psychiatry. 2019;76:749–58.
19. Selim MK, Harel M, De Santis S, Perini I, Sommer WH, Heilig M, et al. Repetitive deep TMS in alcohol dependent patients halts progression of white matter changes in early abstinence. Psychiatry Clin Neurosci. 2024;78:176–85.
20. Warden AS, Wolfe SA, Khom S, Varodayan FP, Patel RR, Steinman MQ, et al. Microglia control escalation of drinking in alcohol-dependent mice: genomic and synaptic drivers. Biol Psychiatry. 2020;88:910–21.
21. Althubaity N, Schubert J, Martins D, Yousaf T, Nettis MA, Mondelli V, et al. Choroid plexus enlargement is associated with neuroinflammation and reduction of blood brain barrier permeability in depression. NeuroImage: Clin. 2022;33:102926.
22. Diez-Cirarda M, Yus-Fuertes M, Delgado-Alonso C, Gil-Martínez L, Jiménez-García C, Gil-Moreno MJ, et al. Choroid plexus volume is enlarged in long COVID and associated with cognitive and brain changes. Mol Psychiatry. 2025;30:2821–2830.
23. Ricigliano VA, Stankoff B. Choroid plexuses at the interface of peripheral immunity and tissue repair in multiple sclerosis. Curr Opin Neurol. 2023;36:214–21.
24. Zhou YF, Huang JC, Zhang P, Fan FM, Chen S, Fan HZ, et al. Choroid plexus enlargement and allostatic load in schizophrenia. Schizophrenia Bull. 2020;46:722–31.
25. Folstein MF, Folstein SE, McHugh PR. Mini-mental state ». A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
26. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993;88:791–804.
27. Beck AT, Steer RA, Brown GK Beck depression inventory-II. San Antonio, TX. 1996;78204-2498.
28. Spielberger CD State-trait anxiety inventory for adults. 1983.
29. Anton RF, Moak DH, Latham PK. The obsessive compulsive drinking scale: a new method of assessing outcome in alcoholism treatment studies. Arch Gen psychiatry. 1996;53:225–31.
30. Bourque P, Beaudette D. Étude psychometrique du questionnaire de dépression de Beck auprès d'un échantillon d'étudiants universitaires francophones. Can J Behavioural Science/Revue canadienne des Sci du Comport. 1982;14:211.
31. Bruchon-Schweitzer M, Paulhan I Le manuel du STAI-Y de CD Spielberger, adaptation française. Paris: ECPA. 1993.
32. Ansseau M, Besson J, Lejoyeux M, Pinto E, Landry U, Cornes M, et al. A French translation of the obsessive-compulsive drinking scale for craving in alcohol-dependent patients: a validation study in Belgium, France, and Switzerland. Eur addiction Res. 2000;6:51–6.
33. Cushman JrP, Forbes R, Lemer W, Stewart M. Alcohol withdrawal syndromes: clinical management with lofexidine. Alcoholism: Clin Exp Res. 1985;9:103–8.
34. Sobell LC, Sobell MB Timeline Follow-Back. In: Litten RZ, Allen JP, éditeurs. Measuring Alcohol Consumption. Totowa, NJ: Humana Press; 1992. 41–72.
35. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis: I. Segmentation and surface reconstruction. Neuroimage. 1999;9:179–94.
36. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33:341–55.
37. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex. 2004;14:11–22.
38. Kühn S, Charlet K, Schubert F, Kiefer F, Zimmermann P, Heinz A, et al. Plasticity of hippocampal subfield volume cornu ammonis 2+3 over the course of withdrawal in patients with alcohol dependence. JAMA Psychiatry. 2014;71:806–11.
39. van Eijk J, Demirakca T, Frischknecht U, Hermann D, Mann K, Ende G. Rapid partial regeneration of brain volume during the first 14 days of abstinence from alcohol. Alcohol Clin Exp Res. 2013;37:67–74.
40. Yen CH, Ho PS, Yeh YW, Liang CS, Kuo SC, Huang CC, et al. Differential cytokine levels between early withdrawal and remission states in patients with alcohol dependence. Psychoneuroendocrinology. 2017;76:183–91.
41. Chen G, Taylor PA, Cox RW. Is the statistic value all we should care about in neuroimaging?. NeuroImage. 2017;147:952–9.
42. de Timary P, Luts A, Hers D, Luminet O. Absolute and relative stability of alexithymia in alcoholic inpatients undergoing alcohol withdrawal: relationship to depression and anxiety. Psychiatry Res. 2008;157:105–13.
43. Adams C, Conigrave JH, Lewohl J, Haber P, Morley KC. Alcohol use disorder and circulating cytokines: a systematic review and meta-analysis. Brain, Behavior, Immun. 2020;89:501–12.
44. Zhang K, Luo J. Role of MCP-1 and CCR2 in alcohol neurotoxicity. Pharmacol Res. 2019;139:360–6.
45. Marshall SA, Geil CR, Nixon K. Prior binge ethanol exposure potentiates the microglial response in a model of alcohol-induced neurodegeneration. Brain Sci. 2016;6:16.
46. Walter TJ, Crews FT. Microglial depletion alters the brain neuroimmune response to acute binge ethanol withdrawal. J Neuroinflammation. 2017;14:86.
47. Girard M, Malauzat D, Nubukpo P. Serum inflammatory molecules and markers of neuronal damage in alcohol-dependent subjects after withdrawal. World J Biol Psychiatry. 2019;20:76–90.
48. Li W, Amet T, Xing Y, Yang D, Liangpunsakul S, Puri P, et al. Alcohol abstinence ameliorates the dysregulated immune profiles in patients with alcoholic hepatitis: a prospective observational study. Hepatology. 2017;66:575–90.
49. D'Esposito V, Di Tolla MF, Lecce M, Cavalli F, Libutti M, Misso S, et al. Lifestyle and dietary habits affect plasma levels of specific cytokines in healthy subjects. Front Nutr. 2022;9:913176.
50. Jung F, Burger K, Staltner R, Brandt A, Mueller S, Bergheim I. Markers of intestinal permeability are rapidly improved by alcohol withdrawal in patients with alcohol-related liver disease. Nutrients. 2021;13:1659.
51. Leclercq S, Matamoros S, Cani PD, Neyrinck AM, Jamar F, Stärkel P, et al. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. PNAS. 2014;111:E4485–93.
52. Levänen B, Glader P, Dahlén B, Billing B, Qvarfordt I, Palmberg L, et al. Impact of tobacco smoking on cytokine signaling via interleukin-17A in the peripheral airways. Int J Chronic Obstr Pulmonary Dis. 2016;11:2109–16.
53. Damkier HH, Brown PD, Praetorius J. Cerebrospinal fluid secretion by the choroid plexus. Physiological Rev. 2013;93:1847–92.
54. Schwartz M, Baruch K. The resolution of neuroinflammation in neurodegeneration: leukocyte recruitment via the choroid plexus. EMBO J. 2014;33:7–22.
55. Kabashima H, Yoneda M, Nagata K, Hirofuji T, Maeda K. The presence of chemokine (MCP-1, MIP-1α, MIP-1β, IP-10, Rantes)-Positive cells and chemokine receptor (CCR5, CXCR3)-Positive cells in inflamed human gingival tissues. Cytokine. 2002;20:70–7.
56. Petzold J, Pochon JBF, Ghahremani DG, London ED. Structural indices of brain aging in methamphetamine use disorder. Drug Alcohol Dependence. 2024;256:111107.
57. Tomasi D, Wiers CE, Manza P, Shokri-Kojori E, Michele-Vera Y, Zhang R, et al. Accelerated aging of the amygdala in alcohol use disorders: relevance to the dark side of addiction. Cereb Cortex. 2021;31:3254–65.

58. Hidaka Y, Hashimoto M, Suehiro T, Fukuhara R, Ishikawa T, Tsunoda N, et al. Association between choroid plexus volume and cognitive function in community-dwelling older adults without dementia: a population-based cross-sectional analysis. Fluids Barriers CNS. 2024;21:101.
59. Santis SD, Cosa-Linan A, Garcia-Hernandez R, Dmytrenko L, Vargova L, Vorisek I, et al. Chronic alcohol consumption alters extracellular space geometry and transmitter diffusion in the brain. Sci Adv. 2020;6:eaba0154.
60. Bach P, Koopmann A, Bumb JM, Vollstädt-Klein S, Reinhard I, Rietschel M, et al. Leptin predicts cortical and subcortical gray matter volume recovery in alcohol dependent patients: A longitudinal structural magnetic resonance imaging study. Hormones Behav. 2020;124:104749.
61. Bühler M, Mann K. Alcohol and the human brain: a systematic review of different neuroimaging methods. Alcoholism: Clin Exp Res. 2011;35:1771–93.
62. Pfefferbaum A, Sullivan EV, Mathalon DH, Shear PK, Rosenbloom MJ, Lim KO. Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. Alcoholism: Clin Exp Res. 1995;19:1177–91.
63. Schroth G, Naegele T, Klose U, Mann K, Petersen D. Reversible brain shrinkage in abstinent alcoholics, measured by MRI. Neuroradiology. 1988;30:385–9.
64. Besson JA. In vivo and in vitro tissue scanning studies in alcoholic brain disease. Alcohol Alcohol Suppl. 1993;2:31–9.
65. Trabert W, Betz T, Niewald M, Huber G. Significant reversibility of alcoholic brain shrinkage within 3 weeks of abstinence. Acta Psychiatr Scand. 1995;92:87–90.
66. Tutus A, Kuğu N, Sofuoğlu S, Nardali M, Şimşek A, Karaaslan F, et al. Transient frontal hypoperfusion in Tc-99m hexamethylpropyleneamineoxime single photon emission computed tomography imaging during alcohol withdrawal. Biol Psychiatry. 1998;43:923–8.
67. Nicolás JM, Catafau AM, Estruch R, Lomeña FJ, Salamero M, Herranz R, et al. Regional cerebral blood flow-SPECT in chronic alcoholism: relation to neuropsychological testing. J Nucl Med. 1993;34:1452–9.
68. Gansler DA, Harris GJ, Oscar-Berman M, Streeter C, Lewis RF, Ahmed I, et al. Hypoperfusion of inferior frontal brain regions in abstinent alcoholics: a pilot SPECT study. J Stud Alcohol. 2000;61:32–7.
69. Harper C, Corbett D. Changes in the basal dendrites of cortical pyramidal cells from alcoholic patients-a quantitative Golgi study. J Neurology, Neurosurg Psychiatry. 1990;53:856–61.
70. Bendszus M, Weijers HG, Wiesbeck G, Warmuth-Metz M, Bartsch AJ, Engels S, et al. Sequential MR imaging and proton MR spectroscopy in patients who underwent recent detoxification for chronic alcoholism: correlation with clinical and neuropsychological data. Am J Neuroradiol. 2001;22:1926–32.
71. Ende G, Welzel H, Walter S, Weber-Fahr W, Diehl A, Hermann D, et al. Monitoring the effects of chronic alcohol consumption and abstinence on brain metabolism: a longitudinal proton magnetic resonance spectroscopy study. Biol Psychiatry. 2005;58:974–80.
72. Köhler S, Klimke S, Hellweg R, Lang UE. Serum brain-derived neurotrophic factor and nerve growth factor concentrations change after alcohol withdrawal: preliminary data of a case-control comparison. Eur Addict Res. 2013;19:98–104.
73. Bartsch AJ, Homola G, Biller A, Smith SM, Weijers HG, Wiesbeck GA, et al. Manifestations of early brain recovery associated with abstinence from alcoholism. Brain. 2007;130:36–47.
74. Zahr NM, Mayer D, Rohlfing T, Hasak MP, Hsu O, Vinco S, et al. Brain injury and recovery following binge ethanol: evidence from in vivo magnetic resonance spectroscopy. Biol Psychiatry. 2010;67:846–54.
75. Gazdzinski S, Durazzo TC, Meyerhoff DJ. Temporal dynamics and determinants of whole brain tissue volume changes during recovery from alcohol dependence. Drug Alcohol Depend. 2005;78:263–73.
76. Deen B, Koldewyn K, Kanwisher N, Saxe R. Functional organization of social perception and cognition in the superior temporal sulcus. Cereb cortex. 2015;25:4596–609.
77. Lusher J, Chandler C, Ball D. Alcohol dependence and the alcohol Stroop paradigm: evidence and issues. Drug Alcohol Depend. 2004;75:225–31.
78. Gaudreault PO, King SG, Malaker P, Alia-Klein N, Goldstein RZ. Whole-brain white matter abnormalities in human cocaine and heroin use disorders: association with craving, recency, and cumulative use. Mol Psychiatry. 2023;28:780–91.
79. Marshall SA, McClain JA, Kelso ML, Hopkins DM, Pauly JR, Nixon K. Microglial activation is not equivalent to neuroinflammation in alcohol-induced neurodegeneration: the importance of microglia phenotype. Neurobiol Dis. 2013;54:239–51.
80. Cruz C, Meireles M, Silva SM. Chronic ethanol intake induces partial microglial activation that is not reversed by long-term ethanol withdrawal in the rat hippocampal formation. NeuroToxicology. 2017;60:107–15.
81. Crews FT, Macht V, Vetreno RP. Epigenetic regulation of microglia and neurons by proinflammatory signaling following adolescent intermittent ethanol (AIE) exposure and in human AUD. Adv Drug Alcohol Res. 2024;4:12094.
82. De Santis S, Selim MK, Canals S Brain microstructure in alcohol addiction: characterization of diffusion-based MRI biomarkers, neuropathological substrates, and functional consequences. In: Mueller S, Heilig M, éditeurs. Alcohol and alcohol-related diseases. Cham: Springer International Publishing; 2023. 493–508.
83. Huang X, Hussain B, Chang J. Peripheral inflammation and blood–brain barrier disruption: effects and mechanisms. CNS Neurosci Ther. 2021;27:36–47.
84. Stokum JA, Kurland DB, Gerzanich V, Simard JM. Mechanisms of astrocyte-mediated cerebral edema. Neurochem Res. 2015;40:317–28.
85. Gursky ZH, Johansson JR, Klintsova AY. Postnatal alcohol exposure and adolescent exercise have opposite effects on cerebellar microglia in rat. Intl J Devlp Neurosci. 2020;80:558–71.
86. Gotkiewicz M, Capra J, Miettinen PO, Natunen T, Tanila H. Three-dimensional view of microglia—amyloid plaque interactions. Glia. 2025;73:196–209.
87. Sanchez-Alavez M, Nguyen W, Mori S, Wills DN, Otero D, Ehlers CL, et al. Time course of microglia activation and brain and blood cytokine/chemokine levels following chronic ethanol exposure and protracted withdrawal in rats. Alcohol. 2019;76:37–45.
88. Zhao YN, Wang F, Fan YX, Ping GF, Yang JY, Wu CF. Activated microglia are implicated in cognitive deficits, neuronal death, and successful recovery following intermittent ethanol exposure. Behavioural Brain Res. 2013;236:270–82.
89. Mokri B. The Monro–Kellie hypothesis. Neurology. 2001;56:1746–8.
90. Tan YL, Yuan Y, Tian L. Microglial regional heterogeneity and its role in the brain. Mol Psychiatry. 2020;25:351–67.
91. Bond DJ, Andreazza AC, Torres IJ, Honer WG, Lam RW, Yatham LN. Association of total peripheral inflammation with lower frontal and temporal lobe volumes in early-stage bipolar disorder: a proof-of-concept study. J Affect Disord. 2022;319:229–34.
92. Radewicz K, Garey LJ, Gentleman SM, Reynolds R. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. J Neuropathol Exp Neurol. 2000;59:137–50.
93. Vicario CM, Nitsche MA, Salehinejad MA, Avanzino L, Martino G. Time processing, interoception, and insula activation: a mini-review on clinical disorders. Front Psychol. 2020;11:1893.
94. Kerezoudis P, Howe CL, Wu LJ, Lundstrom BN, Van Gompel JJ. Insula and the immune system: more than mere co-existence?. Neurosci Bull. 2022;38:1271–3.
95. Bach P, Zaiser J, Zimmermann S, Gessner T, Hoffmann S, Gerhardt S, et al. Stress-Induced sensitization of insula activation predicts alcohol craving and alcohol use in alcohol use disorder. Biol Psychiatry. 2024;95:245–55.
96. Gowin JL, Ball TM, Wittmann M, Tapert SF, Paulus MP. Individualized relapse prediction: Personality measures and striatal and insular activity during reward-processing robustly predict relapse. Drug Alcohol Depend. 2015;152:93–101.
97. Maynard ME, Barton EA, Robinson CR, Wooden JI, Leasure JL. Sex differences in hippocampal damage, cognitive impairment, and trophic factor expression in an animal model of an alcohol use disorder. Brain Struct Funct. 2018;223:195–210.
98. Pascual M, Montesinos J, Marcos M, Torres J, Costa-Alba P, García-García F, et al. Gender differences in the inflammatory cytokine and chemokine profiles induced by binge ethanol drinking in adolescence. Addiction Biol. 2017;22:1829–41.
99. Durazzo TC, Mon A, Pennington D, Abé C, Gazdzinski S, Meyerhoff DJ. Interactive effects of chronic cigarette smoking and age on brain volumes in controls and alcohol-dependent individuals in early abstinence: Interactive effects. Addiction Biol. 2014;19:132–43.
100. Elisia I, Lam V, Cho B, Hay M, Li MY, Yeung M, et al. The effect of smoking on chronic inflammation, immune function and blood cell composition. Sci Rep. 2020;10:19480.
101. Zhang W, Lin H, Zou M, Yuan Q, Huang Z, Pan X, et al. Nicotine in inflammatory diseases: anti-inflammatory and pro-inflammatory effects. Front immunolo. 2022;13:826889.
102. Elbejjani M, Auer R, Jacobs JrDR, Haight T, Davatzikos C, Goff JrDC, et al. Cigarette smoking and gray matter brain volumes in middle age adults: the CARDIA Brain MRI sub-study. Transl psychiatry. 2019;9:78.
103. Ho YS, Yang X, Yeung SC, Chiu K, Lau CF, Tsang AWT, et al. Cigarette smoking accelerated brain aging and induced pre-Alzheimer-like neuropathology in rats. PLoS one. 2012;7:e36752.
104. Torres SR, Fröde TS, Nardi GM, Vita N, Reeb R, Ferrara P, et al. Anti-inflammatory effects of peripheral benzodiazepine receptor ligands in two mouse models of inflammation. Eur J pharmacol. 2000;408:199–211.
105. Zavala F, Taupin V, Descamps-Latscha B. In vivo treatment with benzodiazepines inhibits murine phagocyte oxidative metabolism and production of interleukin 1, tumor necrosis factor and interleukin-6. J pharmacol Exp ther. 1990;255:442–50.
106. Huhtaniska S, Jääskeläinen E, Heikka T, Moilanen JS, Lehtiniemi H, Tohka J, et al. Long-term antipsychotic and benzodiazepine use and brain volume changes in schizophrenia: The Northern Finland Birth Cohort 1966 study. Psychiatry Res: Neuroimaging. 2017;266:73–82.

107. Valmorbida A, Longo GZ, Nascimento GM, Oliveira LL, de, Trindade EBS, et al. Association between cytokine levels and anthropometric measurements: a population-based study. Br J Nutr. 2023;129:1119–26.
108. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. Neurobiol Aging. 2014;35:S20–8.
109. Durazzo TC, Rothlind JC, Gazdzinski S, Meyerhoff DJ. The relationships of sociodemographic factors, medical, psychiatric, and substance-misuse co-morbidities to neurocognition in short-term abstinent alcohol-dependent individuals. Alcohol. 2008;42:439–49.
110. Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14:365–76.
111. Ioannidis JPA. Why most published research findings are false. PLOS Med. 2005;2:e124.
112. Carp J. On the plurality of (methodological) worlds: estimating the analytic flexibility of FMRI experiments. Front Neurosci. 2012;6:149.
113. Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafò MR, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. Nat Rev Neurosci. 2017;18:115–26.

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AUTHOR CONTRIBUTIONS

GP conceived and designed the study, coordinated the project, performed the statistical analyses, and wrote the manuscript. MKS contributed to neuroimaging analyses and interpretation of the results. SC provided expertise in neuroimaging and neuroimmune mechanisms and critically revised the manuscript. PS provided clinical resources and approved the final version of the manuscript. MP contributed to patient recruitment and clinical data collection. LD contributed to MRI data processing, analysis, and interpretation. SL contributed to the interpretation of inflammatory markers and provided expertise in inflammation. PDT supervised the study, contributed to study design and clinical interpretation, and critically revised the manuscript. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from each participant after a full explanation of the study's objectives, procedures, and possible risks. The study protocol was approved by the "Comité d'éthique Hospitalo-facultaire Saint-Luc UCLouvain" (2014/31dec/614). For patients, the capacity to provide informed consent was assessed by trained research staff, and participation was entirely voluntary, with the possibility to withdraw at any time without consequences for treatment.

ADDITIONAL INFORMATION

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