Memory Impairment in Alcohol Use Disorder is Associated with Regional Frontal Brain Volumes

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Abstract

Background: Episodic memory deficits occur in alcohol use disorder (AUD), but their anatomical substrates remain in question. Although persistent memory impairment is classically associated with limbic circuitry disruption, learning and retrieval of new information also relies on frontal systems. Despite AUD vulnerability of frontal lobe integrity, relations between frontal regions and memory processes have been under-appreciated.

Methods: Participants included 91 AUD (49 with a drug diagnosis history) and 36 controls. Verbal and visual episodic memory scores were age- and education-corrected. Structural magnetic resonance imaging (MRI) data yielded regional frontal lobe (precentral, superior, orbital, middle, inferior, supplemental motor, and medial) and total hippocampal volumes.

Results: AUD were impaired on all memory scores and had smaller precentral frontal and hippocampal volumes than controls. Orbital, superior, and inferior frontal volumes and lifetime alcohol consumption were independent predictors of episodic memory in AUD. Selectivity was established with a double dissociation, where orbital frontal volume predicted verbal but not visual memory, whereas inferior frontal volumes predicted visual but not verbal memory. Further,

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superior frontal volumes predicted verbal memory in AUD alone, whereas orbital frontal volumes predicted verbal memory in AUD+drug abuse history.

Conclusions: Selective relations among frontal subregions and episodic memory processes highlight the relevance of extra-limbic regions in mnemonic processes in AUD. Memory deficits resulting from frontal dysfunction, unlike the episodic memory impairment associated with limbic dysfunction, may be more amenable to recovery with cessation or reduction of alcohol misuse and may partially explain the heterogeneity in episodic memory abilities in AUD.

Keywords

alcohol; episodic memory; frontal volumes; orbitofrontal; drug abuse; MRI

1. Introduction

Memory deficits occur in individuals with alcohol use disorder (AUD). Generally, AUD-related deficits are more often observed for episodic memory (past personally experienced events that occurred at a specific time and in a specific place) (Beatty, Katzung, Moreland, & Nixon, 1995; Fama, Le Berre, Sassoon, et al., 2019; Glenn & Parsons, 1992; Oscar-Berman et al., 2014; Parsons & Nixon, 1993; Pitel et al., 2007; Sullivan, Mathalon, Ha, Zipursky, & Pfefferbaum, 1992; Tivis, Beatty, Nixon, & Parsons, 1995) than for semantic (knowing "what"/facts that do not have a specific time or place associated with the memory) (Fama et al., 2011) or implicit (knowing "how" to perform a task or skill) memory (Fama, Pfefferbaum, & Sullivan, 2004; Fama, Rosenbloom, Sassoon, Pfefferbaum, & Sullivan, 2012). Episodic memory deficits are heterogeneous in pattern and severity, ranging from mild in uncomplicated AUD to profound with global amnesia marking alcoholic Wernicke-Korsakoff's syndrome (WKS) (Kopelman, 1995; Victor, Adams, & Colllins, 1989). Factors potentially contributing to the heterogeneity in episodic memory performance in uncomplicated AUD include comorbid non-alcohol substance misuse, which is highly prevalent in AUD (Fein, Smith, & Greenstein, 2012; Grant et al., 2015; Mon et al., 2014; Schmidt, Pennington, Cardoos, Durazzo, & Meyerhoff, 2017).

Although there has been debate about whether memory deficits in AUD are a consequence of executive dysfunction rather than a primary mnemonic deficit, ample evidence supports a genuine episodic memory deficit in individuals with AUD) (Nixon, Tivis, Jenkins, & Parsons, 1998; Oscar-Berman, 1990; Pitel et al., 2007; Pitel, Eustache, & Beaunieux, 2014). A study assessing memory processes (i.e., learning, storage, encoding, and retrieval) and executive function processes (i.e., organization, inhibition, flexibility, updating and integration) in detoxified individuals with AUD reported that, although deficits were observed in both cognitive domains, memory deficits were statistically independent of executive function deficits (Pitel et al., 2007). That study did reveal a relation between fluency and learning, suggesting that executive functions may play a role in mnemonic performance albeit not a predominant one. Thus, despite the relevance of executive functions to cognitive processes in enhancing memory performance, especially retrieval and strategic recall, they did not fully account for the mnemonic deficits of AUD.

Episodic memory processes have classically been associated with integrity of the hippocampus and associated medial temporal and diencephalic structures (Aggleton, 2014; Aggleton & Morris, 2018; Milner, 1958). These limbic structures are integral to Papez circuit. Hippocampal volume deficits occur in AUD (Beresford et al., 2006; Pfefferbaum et al., 2018; Sawyer et al., 2020) and in alcohol-related Wernicke-Korsakoff syndrome (Sullivan & Marsh, 2003). The profound anterograde memory impairment associated with WKS and its underlying neuropathology is in most cases permanent with little to no recovery (Kopelman, 1995). Such severe and permanent episodic memory impairment can occur in other neurological conditions, including herpes simplex encephalitis (Cermak & O'Connor, 1983) and medial temporal lobe epilepsy (Scoville & Milner, 1957), that involve Papez circuit.

The frontal lobes are also relevant to episodic learning and retrieval (Buckner, Kelley, & Petersen, 1999; Kopelman, 1991). Indeed, human (Frey & Petrides, 2000, 2002) and nonhuman primate (Meunier, Bachevalier, & Mishkin, 1997) studies have demonstrated the relevance of orbitofrontal regions to information encoding. Similarly, superior frontal regions associated with working memory processes have been implicated in supporting episodic memory processes (Nissim et al., 2016).

Frontally-based systems may be the most vulnerable of all brain regions to AUD (in vivo: (Durazzo & Meyerhoff, 2020; Oscar-Berman & Hutner, 1993; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997; Pfefferbaum et al., 2018; Sullivan et al., 2018); postmortem: (Courville, 1955; Harper & Kril, 1990). Volume deficits have consistently been reported in orbitofrontal cortex (Durazzo et al., 2011; Shields & Gremel, 2020; Wang et al., 2016) and in other frontal subregions including precentral, superior, middle, inferior, supplementary motor, and medial cortices (Sullivan et al., 2018) in AUD. Taken together, neuropsychological and neuroimaging results indicate a likelihood that frontally-based systems contribute to the genuine mnemonic deficits in AUD, thereby implicating a neural mechanism for selective mnemonic fragility that has been incompletely articulated to date. Further, AUD-drug abuse comorbidity exerts an additional toll on prefrontal cortical volumes, even in those who had been abstinent from substances for more than 2 years (Tanabe et al., 2009), posing an added source of degradation on associated mnemonic functions.

Recently, we reported a selective association between a memory composite score and frontal volumes in AUD, saliently in abstinent individuals with AUD who had a history of a drug abuse diagnosis (Fama, Le Berre, Sassoon, et al., 2019). Those findings were consistent with earlier studies suggesting that integrity of frontal cortical regions, particularly orbitofrontal regions (Frey & Petrides, 2000, 2002), may be critical for memory processes (Buckner et al., 1999). Although we found that AUD had smaller hippocampal volume, on average, compared with the control group, we did not identify an association between hippocampal volume and the memory composite score. Here we expand on our previous findings by separately examining the relations between verbal and visual stimuli and regional frontal gray matter and hippocampal volumes in AUD with and without a drug history for both immediate and delayed recall. We hypothesized that individuals with AUD, regardless of drug history, would show deficits for both verbal and visual stimuli, evident in both

immediate and delayed recall, and that these deficits would be related to selective regional frontal volumes, namely orbital and superior frontal volumes. We speculated that based on previous studies on episodic memory in AUD relations between episodic memory and orbital frontal volumes would be greater in individuals with AUD who had a history of a drug diagnosis than those without such history and that this relation would be stronger for verbal than visual memory and immediate than delayed memory processes.

2. Methods and Materials

2.1 Participants

Participants included 91 individuals with alcohol use disorder (AUD: age 25-70 years; 71 men and 20 women) and 36 healthy controls (CTRL: age 25-73 years; 21 men and 15 women). AUD participants were almost exclusively recruited from local substance abuse treatment programs and sobriety support groups. All AUD participants were both treatment seeking and self-identified as having problems with alcohol misuse and met DSM-IV-TR criteria for alcohol dependence and DSM-5 criteria for AUD. Control participants were recruited from the local community. These participants were a subset of those reported in previous magnetic resonance imaging (MRI) studies (Pfefferbaum et al., 2018; Sullivan et al., 2018) and other reports published by our laboratory that examined the neurological and nutritional factors associated with cognitive and motor deficits in alcoholism (Fama, Le Berre, Hardcastle, et al., 2019; Pitel et al., 2011) and neural correlates of cognitive and motor domains (Fama, Le Berre, Sassoon, et al., 2019). The present paper extends previous reports by delving into specific episodic memory modalities (verbal vs. visual) and processes (immediate vs. delayed) and subregional volumes of the frontal lobe.

Screening for exclusion was based on the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1998) and questionnaires on health status, administered by calibrated research clinicians. Participants were excluded if they had fewer than 8 years of education or a significant history of medical (e.g., epilepsy, stroke, multiple sclerosis, uncontrolled diabetes, or loss of consciousness > 30 minutes), psychiatric (i.e., schizophrenia or bipolar I disorder) or neurological (e.g., neurodegenerative disease) disorder. An additional exclusion criterion for the control group was any DSM-IV-TR Axis I disorder. All participants also underwent a semi-structured timeline follow-back interview to quantify lifetime alcohol consumption (Skinner, 1982; Skinner & Sheu, 1982). Severity of depressive symptoms was assessed with the Beck Depression Inventory-II in all participants (Beck, Steer, & Brown, 1996). This research protocol was approved by the Institutional Review Boards of Stanford University and SRI International. Written informed consent was obtained from all participants, none of whom was clinically demented or conserved.

For the AUD group, the average age of onset of alcohol dependence was 24.1+8.7 years (range=12 to 48 years) and the average length of alcohol dependence was 23.8+11.6 years (range=3 to 51 years). AUD participants drank an average of 1340+1019 kg of alcohol over their lifetime (range=176 to 4711 kg; median=1040 kg). By contrast, controls drank on average 26+35 kg alcohol (range=0 to 136 kg; median=9.5 kg) over their lifetime. Of the 91 AUD participants, 49 (54%) met criteria in their lifetime for at least one non-alcohol substance abuse/dependence diagnosis (*AUD+DrugHx*), whereas 42 (46 %) had no

substance abuse/dependence history besides 9 who had only a past marijuana diagnosis (*AUD-noDrugHx*).

In the AUD group (n=91) average days sober was 109+112 (range = 1 to 726 days); median was 83 days. Time since last met an alcohol diagnosis was on average 28 weeks (sd=42 weeks, range = 0 to 286 weeks, median=14 weeks). At the time of testing, all 91 participants met DSM-IV criteria for alcohol dependence with 65 participants being in early full remission, 7 participants meeting criteria for early partial remission, 1 being in sustained partial remission, 10 being sustained full remission, and 8 participants meeting criteria for current dependence (i.e., within the past month), and 18 reported drinking some amount of alcohol within the past month. Of the 91 AUD participants, 40 participants (44%) met criteria for DSM-5 diagnostic criteria for current AUD (i.e., within the past three months), whereas 51 participants met criteria for past AUD. No AUD participant had ever been diagnosed with Wernicke's encephalopathy nor met criteria for alcohol-induced persisting amnestic disorder. Although the AUD+DrugHx group reported more days without drinking prior to testing than the AUD-noDrugHx group, the differences was not significant [t(89)=1.35, p=.181].

Investigation into individual drug classes indicated that of the 49 AUD participants who met DSM-IV-TR criteria for abuse/dependence for non-alcohol substances besides marijuana: 42 participants met criteria for a cocaine diagnosis, 17 for amphetamines, 13 for opioids, 6 for hallucinogens, 5 for sedatives, and 2 for other substance abuse/dependence. For those AUD participants with a history of cocaine, amphetamine, opioid, hallucinogen, or sedative misuse, all were in remission for at least one month, with an average time since remission of approximately 5.5 years. For nicotine, 46 (51%) of the 91 AUD participants were current tobacco smokers and 17 (19%) were past smokers, whereas 2 of 36 (6%) controls were current smokers and 1 (3%) was a past smoker.

In the AUD group (n=91), 10 participants (11.0%) identified as Hispanic, 2 (2.2%) identified as Native American, 41 (45.1%) identified as Black, and 41 (45.1%) identified as White. No AUD participant identified as either Asian or Islander. In the control group (n=36), 12 participants (33.3%) identified as Black, 16 (44.4%) identified as White, 7 (19.4%) identified as Asian, and 1 (2.8%) was unknown. No control participant identified as Native American or Islander. AUD and CTRL groups differed in percentage of Hispanic and Asian participants. Examination of AUD subgroups with and without a history of a drug diagnosis indicated that these subgroups did not differ significantly on ethnicity.

AUD and CTRL groups did not differ significantly in age or on an IQ estimate derived from the National Adult Reading Test (NART) (Nelson, 1982) (see Table 1). On average, the AUD group had fewer years of education and scored lower on a screening test of overall current cognitive level (Dementia Rating Scale-2) (Mattis, 2004) than the CRTL group; no AUD participant was clinically demented. The AUD group also endorsed a greater level of depressive symptoms (BDI-II) and as expected consumed far more alcohol over their lifetime than the CTRL group. There were significantly a greater proportion of women in the AUD group compared with the CTRL group (Chi-square=4.8, p=.03).

2.2 Neurocognitive Testing: Verbal and Visual Episodic Memory

Logical Memory Stories from the Wechsler Memory Scale – Revised (Wechsler, 1987).—The examinee is read a short narrative and asked to recall the story back to the examiner, using as close to the same words as were read aloud, both immediately after the story was read **(LMI – Immediate Logical Memory)** and then again after a 30-minute delay **(LMII – Delayed Logical Memory).** There are two narratives. The dependent score is the number of details recalled in the immediate and then the delayed conditions (maximum = 50 points for each condition).

Rey-Osterrieth Complex Figure Test (Rey, 1942).—The examinee is shown a complex figure and asked to copy it as accurately and as quickly as possible. After copy is complete, the examinee is asked to draw the complex figure from memory **(Rey-O Imm)**. There is no time limit. The examinee is asked again to draw the complex figure from memory after a 30-minute delay **(Rey-O Delay)**. Score is number of details recalled per standard scoring instructions on immediate and then delayed condition (maximum = 36 points for each condition).

2.3 Magnetic Resonance Image (MRI): Data Acquisition and Processing

MRI data were acquired on 3 Tesla GE whole body MR systems (General Electric Healthcare, Waukesha, WI) using an 8-channel phased-array head coil. T1-weighted Inversion-Recovery Prepared SPGR images (TR=6.55/5.92 ms, TE=1.56/1.93 ms, TI=300/300 ms, matrix = 256x256, thick=1.25 mm, skip=0 mm, 124 slices) were based on an axial structural sequence that was used for volumetric analysis. Drift was corrected by adjusting scanner calibration parameters when necessary to maintain spatial stability within manufacturer guidelines, and routine phantom data were used to evaluate spatial fidelity.

Preprocessing of the T1-weighted MRI data (124 slices, matrix=256x256, thickness=1.25mm, skip=0) involved noise removal (Coupe et al., 2008), correcting field inhomogeneity via N4ITK (Tustison, Avants, Siqueira, & Gee, 2011), and segmenting the brain mask by majority voting (Rohlfing, Brandt, Menzel, & Maurer, 2004). The voting was performed with respect to the maps generated by separately applying FSL BET (Smith, 2002), AFNI 3dSkullStrip (COX 1996), FreeSurfer mri_gcut (Sadananthan, Zheng, Chee, & Zagorodnov, 2010), and the Robust Brain Extraction (ROBEX) method (Iglesias, Liu, Thompson, & Tu, 2011) to the bias and non-bias corrected T1-weighted MRIs.

Brain tissue segmentation (gray matter, white matter, and cerebrospinal fluid) of the skull-stripped T1-weighted MRI was generated via Atropos (Avants et al., 2011). The label map was further parcellated into the regions defined by the SRI24 atlas (Rohlfing, Zahr, Sullivan, & Pfefferbaum, 2010) by non-rigidly registering the atlas to the MRI via ANTS (Avants, Epstein, Grossman, & Gee, 2008). Frontal gray matter was parcellated into seven regions of interest (ROIs): precentral, superior, orbital, middle, inferior, supplemental motor, and medial (Figure 1). Total hippocampal volume was also calculated. Automatic labeling was always visually inspected for accuracy by a trained research scientist. All brain volumes used in analyses were age- and head-size corrected.

2.4. Statistical analysis

Scores for the memory measures were age- and education-corrected and standardized on the CTRL group [Z-score of CTRL group: mean=0, standard deviation=±1]. CTRL men and women did not differ significantly on any memory score or brain volume measure and were thus collapsed into a single control group. Using Z-scores allowed for direct comparison across test scores within and between groups, which were assessed with 2-tailed t-tests. Cohen's d was calculated for significant group differences. Correlational analyses were conducted to assess the relation between brain and behavioral measures. A False Discovery Rate was employed based on four comparisons (memory scores), requiring the smallest p-value across memory scores to be equal to or less than .0125 to be deemed significant (Benjamini & Hochberg, 1995). Multiple regression models were conducted to assess the amount of variance accounted for by brain ROIs that demonstrated a relation with a memory score based on the zero-order correlational analyses. Planned secondary analyses were conducted to test for differences in brain-behavior relations in individuals with AUD with and without a drug history. Post-hoc analyses, including nonparametric analyses and additional comparisons examining other subgroups of AUD participants (based on DSM-IV and DSM-5 criteria), were also conducted.

3. Results

Raw scores for verbal and visual immediate and delayed episodic memory measures for the AUD and CTRL groups are presented in Table 2.

3.1 Verbal and visual memory Z-scores (immediate and delayed)

The AUD group scored lower than the CTRL group on all verbal and visual memory scores [LMI: t(125)=3.91, p=.0002, Cohen's d=.70; LMII: t(125)=4.19, p<.0001, Cohen's d=.75; Rey-O Imm: t(125)=3.89, p=.0002, Cohen's d=.70; Rey-O Delay: t(125)=2.94, p=.004, Cohen's d=.53] (Figure 2). Differences were significant with FDR correction for multiple comparisons.

3.2. Regional frontal and hippocampal volumes

A group difference emerged for precentral frontal and hippocampal volumes, with AUD having smaller precentral frontal [t(125)=3.13, p=.002, Cohen's d=.63] and hippocampal [t(124)=2.10, p=.038, Cohen's d=.39] volumes than CTRL. Group differences were not observed for superior, orbital, middle, inferior, supplementary motor, or medial frontal volumes (Table 3).

3.3. Correlations between verbal and visual memory scores and regional frontal and hippocampal volumes in AUD

LMI and LMII scores correlated with orbital frontal volume [(n=91), LMI r=.39, p=.0001; LMII r=.43, p<.0001] (Table 4). By contrast, Rey-O Imm and Rey-O Delay scores correlated with inferior frontal volume [Rey-O Imm r=.32, p=.002; Rey-O Delay r=.30, p=.004] (Figure 3). Rey-O Delay score also correlated with superior [r=.28, p=.006] and orbital [r=.25, p=.015] frontal volumes. Scores on these memory tests did not correlate with hippocampal volume.

A multiple regression model predicting Rey-O Delay score from the 3 regions that showed significant zero-order correlations (i.e., inferior, superior, and orbital frontal volumes) indicated that although they accounted for 10.1% of the variance no single region was an independent predictor of this score.

3.4 Correlations between alcohol-related consumption variables and BDI-II and memory scores

Total lifetime alcohol consumption (kg) correlated with each of the verbal and visual memory scores in AUD (n=91: LMI: r=−.35, p=.0008; LMII: r=−.36, p=.0005; Rey-O Imm: r=−.29, p=.005; Rey-O Delay: r=−.21, p=.043) (Figure 4). By contrast, age of alcohol onset, time since last met alcohol diagnosis, and days since last drink were not correlated with any of the memory scores. BDI-II scores were not significantly correlated with any of the memory scores.

Indeed, total lifetime alcohol consumption was an independent predictor of LMI, LMII, and Rey-O Imm scores, when entered into a model with relevant regional brain volumes (Table 5). Total lifetime alcohol consumption accounted for 7.5% of LMI score variance beyond the contribution of orbital frontal volume, which accounted for 11.2% of the variance. Total lifetime alcohol consumption accounted for 7.9% of LMII score variance beyond the contribution of orbital frontal volume, which accounted for 13.8% of the variance. Finally, total lifetime alcohol consumption accounted for 5.9% of Rey-O Imm score variance beyond the contribution of inferior frontal volume, which accounted for 7.4% of the variance.

3.5.1 AUD subgroups based on lifetime drug diagnosis history—

AUD+DrugHx (n=49) did not differ significantly from *AUD-noDrugHx* (n=42) in age, years of education, estimate of premorbid IQ, total lifetime alcohol consumed, severity of depressive symptoms reported, or current general cognitive ability (Table 6).

3.5.2 Memory scores and regional frontal and hippocampal volumes—

AUD+DrugHx had lower scores than *AUD-noDrugHx* on Rey-O Imm [t(89)=2.34, p=.02, Cohen's d=.49], but the subgroups did not differ on LMI [t(89)=.07, p=.94], LMII [t(89)=.03, p=.80], or Rey-O Delay [t(89)=1.03, p=.31] scores. The *AUD+DrugHx* group had smaller precentral [t(89)=2.27, p=.026, Cohen's d=.48] and supplementary motor [t(89)=2.21, p=.029, Cohen's d=.47] frontal volumes and modestly smaller inferior frontal volumes [t(89)=1.97, p=.052, Cohen's d=.42] than the *AUD-noDrugHx group*. AUD subgroups did not differ on hippocampal volume [t(89)=.82, p=.41].

3.5.3. Correlations between memory scores and regional frontal and hippocampal volumes—In the *AUD-noDrugHx* subgroup, LMI and LMII scores correlated with orbital (LMI r=.30, p=.05; LMII r=.36, p=.02) and superior (LMI r=.40, p=.008; LMII r=.32, p=.038) frontal volumes (Table 6). No significant correlations emerged between Rey-O Imm or Rey-O Delay scores and any regional frontal ROI in this subgroup. None of the memory scores correlated with hippocampal volume in the AUD-noDrugHx subgroup.

Multiple regression analyses examined the independent contributions of superior and orbital frontal volumes as predictors of verbal memory scores in *AUD-noDrugHx* (Table 7). Superior frontal volume was an independent predictor, beyond the contribution of orbital frontal volume, for LMI score, accounting for 11.7% of the score variance (Figure 5). By contrast, orbital frontal volume was an independent predictor, beyond the contribution of superior frontal volume, for LMII scores, accounting for 10.5% of the score variance.

In the *AUD+DrugHx*, verbal memory scores correlated with orbital frontal volume (LMI: r=.47, p=.001; LMII: r=.49, p=.000) (Table 1). In contrast with *AUD-noDrugHx*, superior frontal volume was not an independent predictor of LMI in the *AUD+DrugHx*; indeed, superior frontal volume was not correlated with LMI in *AUD+DrugHx* and accounted for less than 1% of the variance in score after the contribution of orbitofrontal volume was taken into account (Figure 5). The Rey-O Imm score correlated with inferior frontal volume (r=.32, p=.024), and Rey-O Delay score correlated with orbital (r=.39, p=.005) and inferior (r=.29, p=.044) frontal volumes in *AUD+DrugHx*. Multiple regression analysis indicated that orbital frontal volume (p=.01), but not inferior frontal volume, was an independent predictor of Rey-O Delay score, accounting for 12.5% of the variance. None of the memory scores correlated significantly with hippocampal volume in the *AUD+DrugHx* subgroup.

Although the drug use in the AUD+DrugHx subgroup varied among participants, 42 of these participants (86%) had a lifetime cocaine diagnosis (37 had a diagnosis of past cocaine dependence and 5 had a diagnosis of past cocaine abuse). Post-hoc analyses for this subgroup of AUD+DrugHx who shared a history of cocaine misuse indicated that the pattern of results reported for the entire group of 49 AUD+DrugHx did not change when only these 42 AUD participants were included in the analyses [orbitofrontal volume and LMI r=.49, p=.0009; orbitofrontal volume and LMII r=.51, p=.0007; orbitofrontal volume and Rey-O Imm r=.33, p=.032; orbitofrontal volume and Rey-O Delay r=.43, p=.004]. In addition, post-hoc analyses indicated that the 9 people with AUD with only a lifetime marijuana diagnosis performed as well as controls on all memory measures; when these AUD participants were excluded from the analyses, group differences between AUD+DrugHx and AUD-noDrugHx and the brain-behavior relations reported endured.

3.5.4.   Correlations between alcohol consumption and BDI-II scores and memory scores in AUD subgroups—Lifetime alcohol consumption (kg) correlated with LMI (r=−.32, p=.040) and Rey-O Imm (r=−.32, p=.038) scores in *AUD-noDrugHx*. In *AUD+DrugHx*, lifetime alcohol consumption correlated with LMI (r=−.39, p=.006) and LMII (r=−.44, p=.002) scores. Multiple regression indicated that lifetime alcohol consumption was an independent predictor of LMI and LMII scores in *AUD+DrugHx*, accounting for 8.2% of the variance in LMI score and 11.1% of the variance in LMII score. BDI scores were not correlated with any of the memory scores in either the AUD-noDrugHx or AUD+DrugHx subgroups.

4.   Discussion

In support of our hypotheses and consistent with earlier studies (Fama, Rosenbloom, Nichols, Pfefferbaum, & Sullivan, 2009; Glenn & Parsons, 1992; Pitel et al., 2007; Tivis

et al., 1995), verbal and visual episodic memory deficits were evident in individuals with AUD compared with healthy control participants. The current results further reveal that performance levels of AUD participants involving verbal and visual episodic memory were selectively related to volumes of orbital, inferior, and superior frontal regions but not to other frontal regions (precentral, middle, supplementary motor, or medial frontal). Selectivity between modalities revealed a double dissociation: orbital but not inferior frontal volumes predicted immediate verbal memory, whereas inferior but not orbital frontal volumes predicted immediate visual memory in AUD. Memory scores were not related to hippocampal volume in AUD.

4.1 Frontal systems of episodic memory processes

A critical and essential role for the frontal neocortex in encoding new experiences (Shallice et al., 1994; Takehara-Nishiuchi, 2020; Tulving, Markowitsch, Craik, Habib, & Houle, 1996) and retrieval of information (Eichenbaum, 2017) has been highlighted in human and animal studies. Among the frontal subregions examined herein, orbital frontal volume was related to episodic memory in AUD, comporting with other reports of the contribution of orbital frontal regions to processes involving consolidation and retrieval of episodic memory (Buckner et al., 1999; Frey & Petrides, 2000, 2002). This finding was robust and present even when post-hoc analyses were conducted on subsets of AUD participants divided by recency of drinking history: actively drinking participants according to DSM-5 (n=41), participants who were in early full remission according to DMS-IV (n=65) or early partial remission (n=7). These post-hoc analyses excluded 8 participants who were currently drinking and 10 participants who were in sustained full remission, having last met criteria for an alcohol diagnosis 2.5 to 12.3 months prior to testing or were in sustained partial remission.

Insofar as there is reported recovery of frontal lobe function with abstinence of curtailed drinking (Meyerhoff & Durazzo, 2020), the relation between orbital frontal volume and episodic memory in AUD raises the speculation that frontally-based episodic memory dysfunction in AUD may be amenable to recovery. Whereas the memory deficits associated with limbic dysfunction (medial temporal and diencephalic structures) have been reported to be relatively stable, memory deficits associated with frontal dysfunction have been shown to be more amenable to change over time. For instance, frontal lobe involvement has also been implicated in the profound anterograde episodic memory deficit associated with transient global amnesia (Guillery-Girard et al., 2004; Le Pira et al., 2005) with recovery of episodic memory processes generally within 24 hours, again supporting the role of extra-hippocampal regions as critical nodes of episodic memory function. The possibility of recovery in uncomplicated AUD is in contrast to the limited recovery observed in anterograde episodic memory arising from Papez circuit dysfunction as occurs in alcohol-related Wernicke-Korsakoff syndrome (Victor et al., 1989). Indeed, recovery of selective cognitive processes, including memory processes, in AUD can take place over years (Nixon & Lewis, 2020). Apart from acute recovery after initial abstinence, evidence for brain recovery from studies based on structural and functional imaging (Oscar-Berman et al., 2014; Pitel et al., 2014) and cognitive performance is documented well past the initial 30-days post abstinence period (Fein & Fein, 2013). Recovery of component

cognitive processes involving episodic memory, including working memory as associated with prefrontal cortical integrity (Romanski, 2004), may contribute to the heterogeneity in severity of mnemonic deficits observed in AUD.

4.2 Alcohol and drugs

Total lifetime alcohol consumption was an independent predictor of verbal and visual episodic memory in AUD, accounting for upwards of 16% of the variance of memory scores. Although the relation between total lifetime alcohol consumption and severity of cognitive deficits in AUD has often been elusive, higher lifetime alcohol consumption was consistently related to poorer verbal and visual memory performance in this study and supports the assumption that alcohol was a principal agent exerting untoward effects on the brain and performance.

Occurrence of drug misuse in AUD was associated with worse immediate visual memory and smaller precentral, inferior, and supplementary motor frontal volumes than in AUD without a past drug abuse diagnosis. Orbitofrontal volume was related to immediate and delayed verbal episodic memory in both AUD with and without a history of a drug abuse diagnosis and to delayed visual memory in AUD with a history of a drug abuse diagnosis. This relation endured in post-hoc analyses including on those AUD with a history of a cocaine diagnosis. Similar relations were also reported in individuals with polysubstance use, specifically alcohol, cocaine, and amphetamine (Tanabe et al., 2009). These results extend reports of orbitofrontal dysregulation associated with general substance misuse (Moorman, 2018; Volkow & Fowler, 2000) yet with selective effects on verbal episodic memory.

Subgroup differences in brain-behavior relations did arise with superior frontal volume as an independent predictor of immediate verbal memory in AUD without a drug abuse diagnosis history, whereas orbital frontal volume was an independent predictor of immediate verbal memory in AUD with a history of a drug abuse diagnosis. Indeed, superior frontal regions have been associated with working memory (du Boisgueheneuc et al., 2006), a component process that supports episodic memory. This finding is consistent with others noting differential effects on brain structure of polysubstance misuse of just one substance (Meyerhoff, 2017) and provides evidence for a role of superior frontal regions in encoding of verbal information in AUD without complications of a drug abuse diagnosis history.

4.3 Limitations

Among the limitations of this study, examination of episodic memory processes was based on only single measures of verbal and one visual memory and requires replication using other or additional mnemonic measures of these processes. Absence of a relation between episodic memory scores and hippocampal volume in this study may be due to imaging limitations precluding measurement of hippocampal subfields. Imaging limitations also precluded us from examining possible relations between diencephalic structures, namely selective nuclei of the thalamus, which have been implicated in memory function in AUD (Pitel, Segobin, Ritz, Eustache, & Beaunieux, 2015), and memory scores. Other limitations include the absence of exact dosage of non-alcohol substances and pattern of use of these

substances throughout a lifetime and differences in percentage of Asian and Hispanic participants between the groups. Further, restricted sample sizes constrained statistical exploration of the effects of specific drug misuse on the frontal-memory relations observed.

5. Conclusion

Taken together, this study highlights the role of selective frontal cortical sites in supporting encoding and retrieval processes of episodic memory in AUD, with a double dissociation observed between verbal and visual stimuli and regional frontal volumes. In addition, the pattern of brain-mnemonic relations in AUD differed with the presence versus absence of history of a drug abuse diagnosis. Both sets of results highlight the relevance and selectivity of frontal sites in disrupting episodic memory functions in AUD. Given the permanence of mnemonic impairment typically following limbic lesions, the extra-limbic, frontal substrate of the AUD-related impairment may have favorable implications for functional recovery with reduction in drinking (cf., Meyerhoff and Durazzo 2020).

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Highlights:

- Verbal and visual episodic memory are impaired in AUD

- Frontal but not hippocampal regions were independent predictors of episodic memory

- Frontal-memory relations in AUD differed with drug-abuse history

- Lifetime alcohol consumption predicted episodic memory deficit severity

- Frontally (rather than limbic)-based memory dysfunction in AUD may be remediable

7 Frontal Cortical Regions
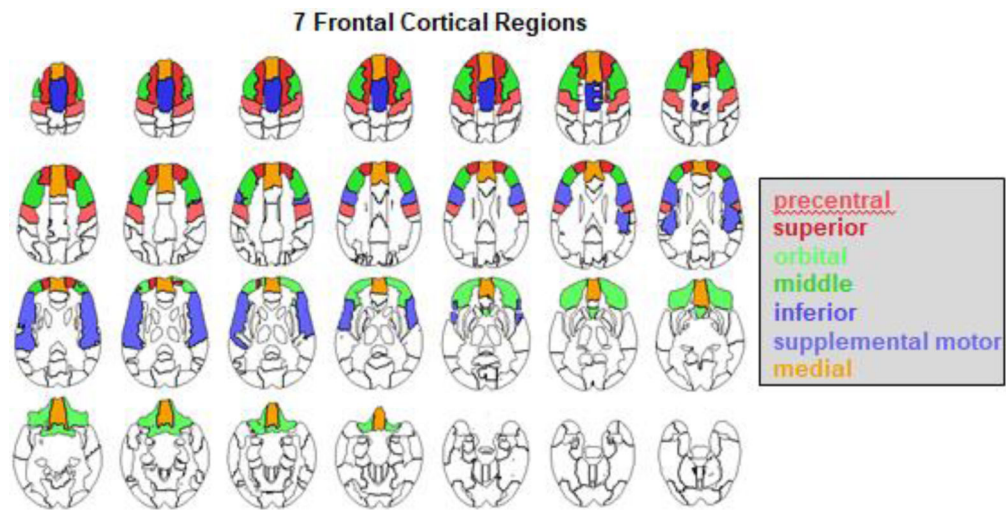
Figure 1:
Color-coded atlas identifying frontal cortical subregions: precentral, superior, orbital, middle, inferior, supplementary motor, and medial.
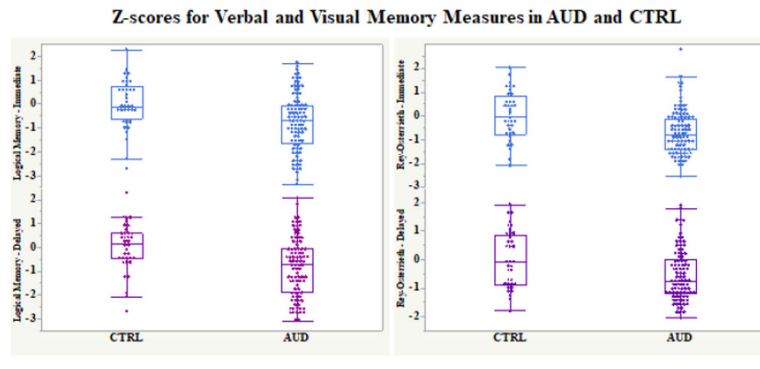
Figure 2:
Box plots depicting verbal (Logical Memory Narratives) and visual (Rey-Osterrieth Complex Figure) immediate and delayed age- and education-corrected memory Z-scores for AUD and CTRL (mean=0, sd=1) groups.
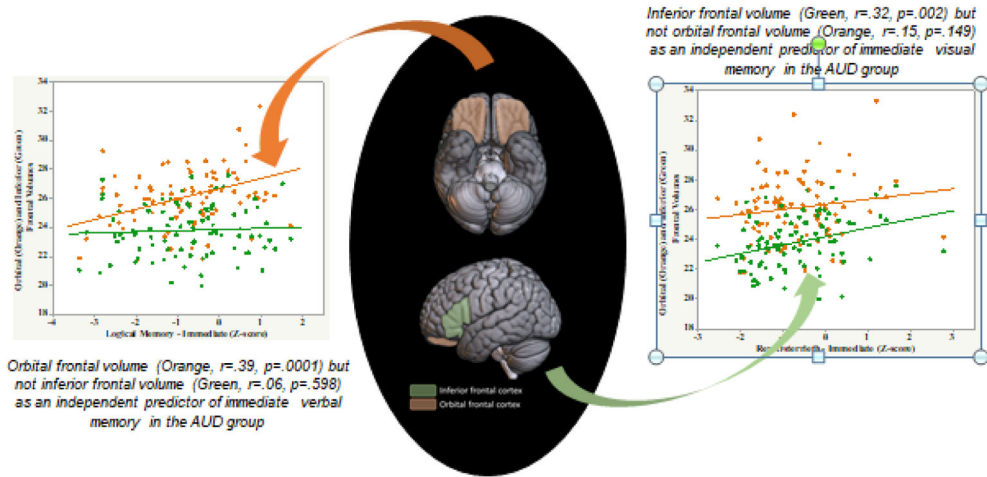
Figure 3:
Dissociable structural brain correlates for immediate verbal and immediate visual memory: evidence of a double dissociation in AUD (n=91).
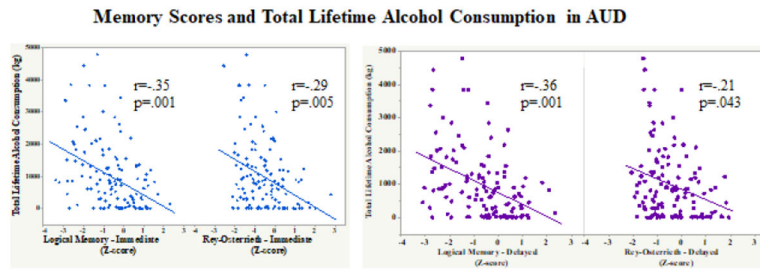
Figure 4:
Scatterplots depicting the relation between total lifetime alcohol consumption (kg) and immediate and delayed verbal (Logical Memory) and visual (Rey-Osterrieth) memory scores in AUD.
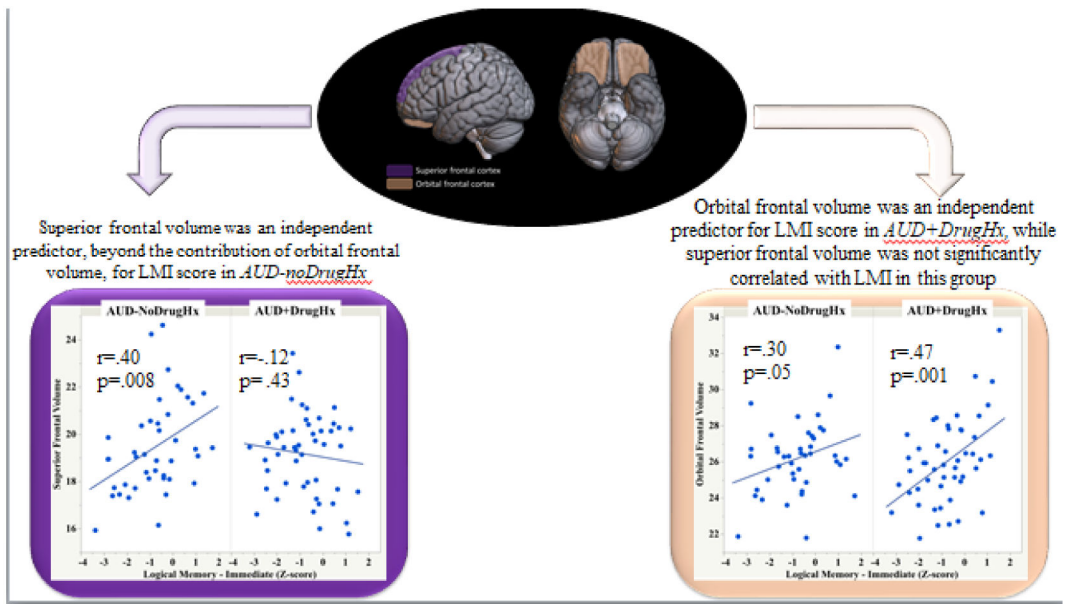
Figure 5:
Immediate verbal memory scores and orbital frontal and superior frontal volumes in AUD with and without a drug diagnosis history - LMI: Logical Memory – Immediate score, Wechsler Memory Scale – Revised.

Table 1

Demographic characteristics of Participant Groups: AUD, CTRL, and AUD subgroups with and without history of drug dx (mean, sd, range)

| Group	Group	Group	Group	Group	Group consumption (kg)	Group	DRS-2[c]
AUD	20 F, 71 M	48.5	13.0	106.7	1340	9.8	135.9
	(n=91)	(10.6)	(2.3)	(9.1)	(1019)	(6.7)	(5.2)
		25 to 70	9 to 21	91 to 124	178 to 4783	0 to 38	121 to 144
CTRL	15 F, 21 M	47.2	15.5	110.7	26	3.1	139.3
	(n=36)	(12.9)	(2.6)	(9.5)	(35)	(3.9)	(2.2)
		25 to 73	11 to 21	92 to 126	0 to 136	0 to 16	135 to 144
Group Differences	**p=.03**	**p=.60**	**p<.0001**	**p=.09**	**p<.0001**	**p<.0001**	**p=.0002**
95% CI		[5.6, −3.2]	[−1.6, −3.5]	[0.6, −8.6]	[1651, 977]	[9.1, 4.3]	[−1.6, −5.2]
AUD subgroups:							
AUD-noDrugHx	12 F, 30 M	46.3	13.2	108.3	1148	8.7	135.6
	(n=42)	(11.1)	(2.2)	(9.0)	(786)	(6.3)	(5.9)
		25 to 69	11 to 21	91 to 124	181 to 3847	0 to 24	121 to 144
AUD+DrugHx	8 F, 41 M	50.3	12.8	104.8	1505	10.7	136.2
	(n=49)	(9.8)	(2.3)	(9.1)	(1166)	(6.9)	(4.6)
		26 to 67	9 to 21	91 to 124	178 to 4783	0 to 38	123 to 143
Group Differences	**ns**	**p=.07**	**p=.38**	**p=.21**	**p=.10**	**p=.16**	**p=.62**
95% CI		[8.4, −0.4]	[0.5, −1.4]	[2.1, −9.1]	[779, −64]	[4.9, −0.9]	[2.8, −1.7]

[a]NART – National Adult Reading Test [AUD n=43, CTRL n=26, AUD-noDrugDx n=23, AUD+Drug Dx n=20]

[b]BDI-II – Beck Depression Inventory – Second Edition

[c]DRS-2 – Dementia Rating Scale – Second Edition

Table 2

Raw scores (mean, sd, range) of memory tests

	AUD N=91	CTRL N=36
Verbal Memory		
Logical Memory - I (Immediate)	20.6 (8.6)	26.9 (7.1)
(max=50)	2 to 37	8 to 39
Logical Memory - II (Delayed)	16.1 (8.7)	22.9 (1.1)
(max=50)	1 to 35	5 to 34
Visual Memory		
Rey-Osterrieth Figure - Immediate	10.9 (5.3)	15.0 (5.6)
(max=36)	0 to 29	4.5 to 26.5
Rey-Osterrieth Figure - Delayed	11.3 (4.9)	14.3 (5.8)
(max=36)	2.5 to 23.5	5 to 24.5

Table 3

ICV- and Age-corrected Brain Volumes (cc) for CTRL, AUD, AUD-noDrugHx, and AUD+DrugHx (mean, sd)

	CTRL	AUD	t, p-value	AUD-noDrugHx	AUD+DrugHx	t, p-value: AUD subgroups
Frontal ROIs	(n=36)	(n=91)		(n=42)	(n=49)	
precentral	18.51	17.38	**t=3.13, p=.002**	17.86	16.96	**t=2.72, p=.026**
	(1.65)	(1.91)		(1.70)	(2.00)	
superior	19.21	19.29	t=0.24, p=.808	19.45	19.16	t=0.76, p=.450
	(1.46)	(1.81)		(1.96)	(1.69)	
orbital	26.38	26.10	t=0.69, p=.490	26.19	26.03	t=0.35, p=.726
	(1.77)	(2.14)		(1.96)	(2.31)	
middle	25.92	25.18	t=1.80, p=.074	25.23	25.14	t=0.20, p=.840
	(1.88)	(2.16)		(2.05)	(2.26)	
inferior	24.14	23.78	t=1.09, p=.277	24.16	23.45	t=1.97, p=.052
	(1.49)	(1.75)		(1.57)	(1.84)	
supplementary motor	11.45	11.18	t=1.04, p=.299	11.51	10.90	**t=2.21, p=.029**
	(1.12)	(1.34)		(1.24)	(1.37)	
medial	24.91	24.69	t=0.66, p=.511	24.99	24.44	t=1.65, p=.102
	(1.85)	(1.59)		(1.54)	(1.61)	
Hippocampus	8.76	8.51	**t=2.10, p=.038**	8.46	8.55	t=0.82, p=.413
	(0.72)	(0.56)		(0.56)	(0.56)	

Table 4

Correlations Between Memory Scores and Regional Frontal Volumes in AUD

	Log Mem I	Log Mem II	Rey-O Imm	Rey-O Delay
Frontal subregions	r=	r=	r=	r=
precentral	−.10	−.06	−.05	.16
superior	.15	.11	.22	**.28**
orbital	**.39**	**.43**	.15	**.25**
middle	−.10	−.10	.06	.09
inferior	.06	.13	**.32**	**.30**
supplemental motor	.06	.05	−.01	.02
medial	−.09	−.12	.07	.13
Hippocampus	−.10	−.07	−.09	−.04

Bold indicates correlations met False Discovery Rate with initial p value = .0125

Log Mem I = Logical Memory Immediate; Log Mem II = Logical Memory Delayed

Rey-O Imm = Rey-Osterrieth Figure Immediate; Rey-O Delay = Rey-Osterrieth Figure Delayed

Table 5

Multiple regression models predicting memory scores from brain volumes and lifetime alcohol consumption in AUD

	t-Ratio	p-value
LM-I		
orbital	**3.58**	**.001**
lifetime alcohol (kg)	**−2.93**	**.004**
LM-II		
orbital	**4.07**	**.000**
lifetime alcohol (kg)	**−3.08**	**.003**
Rey-O Immediate		
inferior	**2.78**	**.007**
lifetime alcohol (kg)	**−2.48**	**.015**
Rey-O Delayed		
superior	1.23	.224
orbital	1.21	.230
inferior	1.33	.188
lifetime alcohol (kg)	−1.43	.155

Bold values denote significance

Table 6

Correlations between Memory Scores and Regional Brain Volume

LMI	No Drug Dx History N=42		Drug Dx History N=49	
	r	p-value	r	p-value
Frontal regions				
precentral	−.209	.18	−.019	.89
superior	**.402**	**.01** *	.115	.43
orbital	**.304**	**.05** *	**.473**	**.00**

LMI	No Drug Dx History N=42		Drug Dx History N=49	
	r	p-value	r	p-value

LMI	No Drug Dx History N=42		Drug Dx History N=49	
	r	p-value	r	p-value
Frontal regions				
precentral	−.209	.18	−.019	.89
superior	**.402**	**.01** *	.115	.43
orbital	**.304**	**.05** *	**.473**	**.00**
middle	−.047	.77	−.014	.33
inferior	.070	.66	.051	.73
supplemental motor	.101	.52	.038	.80
medial	−.104	.51	−.081	.58
Hippocampus	−.004	.98	−.194	.18
LMII				
Frontal regions				
precentral	−.165	.30	.008	.95
superior	**.321**	**.04** *	−.101	.49
orbital	**.363**	**.02** *	**.491**	**.00**
middle	.035	.83	−.201	.17
inferior	.111	.48	.133	.36
supplemental motor	.070	.66	.027	.85
medial	−.176	.26	−.087	.55
Hippocampus	.042	.79	−.163	.26
Rey-O Immediate				
Frontal regions				
precentral	−.212	.18	−.027	.85
superior	.236	.13	.176	.23
orbital	.037	.82	.253	.08
middle	−.051	.75	.170	.26
inferior	.245	.12	**.322**	**.02**
supplemental motor	−.152	.34	.019	.90

	No Drug Dx History N=42		Drug Dx History N=49	
LMI	**r**	**p-value**	**r**	**p-value**
medial	−.067	.68	.132	.37
Hippocampus	−.045	.78	−.104	.48
Hippocampus	−.044	.78	−.010	.94

Bold values denote significance:

*
p<.05

**
p<.01

Table 7

Multiple regression models predicting memory score

	No Drug Diagnosis History	
	t-Ratio	p-value
LMI		
orbital	1.47	.151
superior	**2.16**	**.037**
total lifetime alcohol (kg)	−1.70	.097
LMII		
orbital	2.00	.052
superior	1.51	.141
total lifetime alcohol (kg)	−1.24	.223
	Drug Diagnosis History	
	t-Ratio	p-value
LMI		
orbital	**3.19**	**.003**
total lifetime alcohol (kg)	**−2.33**	**.024**
LMII		
orbital	**3.36**	**.002**
total lifetime alcohol (kg)	**−2.81**	**.007**
ReyO-Imm		
inferior	**2.22**	**.031**
total lifetime alcohol (kg)	−1.53	.132
ReyO-Delay		
orbital	**2.49**	**.017**
inferior	1.71	.094
total lifetime alcohol (kg)	−0.05	.608

Bold values denote significance: p .05