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An Examination of Behavioral and Neuronal Effects of Comorbid Traumatic Brain Injury and Alcohol Use

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Abstract

Background—Chronic alcohol use disorders (AUD) and traumatic brain injury (TBI) are highly comorbid and share commonly affected neuronal substrates (i.e., prefrontal cortex, limbic system and cerebellum). However, no studies have examined how combined physical trauma and heavy drinking affects neurocircuitry relative to heavy drinking alone.

Methods—The current study therefore investigated whether comorbid AUD and mild/moderate TBI (AUD+TBI) would negatively affect maladaptive drinking behaviors (N=90 AUD+TBI; 62 AUD) as well as brain structure (i.e., increased atrophy; N=62 AUD+TBI; 44 AUD) and function (i.e., activation during gustatory cue reactivity; N=55 AUD+TBI; 37 AUD) relative to AUD alone.

Results—Participants reported a much higher incidence of trauma (59.2%) compared to the general population. There were no differences in demographic and clinical measures between groups, suggesting that they were well-matched. Although maladaptive drinking behaviors tended to be worse for the AUD+TBI group, effect sizes were small and not statistically significant. Increased alcohol-cue reactivity was observed in bilateral anterior insula/orbitofrontal cortex,

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anterior cingulate, medial prefrontal cortex, posterior cingulate cortex, dorsal striatum, thalamus, brainstem and cerebellum across both groups relative to a carefully matched appetitive control. However, there were no significant differences in structural integrity or functional activation between AUD+TBI and AUD patients, even when controlling for AUD severity.

Conclusions—Current results indicate that a combined history of mild/moderate TBI was not sufficient to alter drinking behaviors and/or underlying neurocircuitry at detectable levels relative to heavy drinking alone. Future studies should examine the potential long-term effects of combined alcohol and trauma on brain functioning.

Keywords

traumatic brain injury; alcohol use disorders; structure; alcohol-cue reactivity; prefrontal; limbic

Introduction

Acute substance use/intoxication (i.e., day-of-injury drinking) is a well-known risk factor for increasing the likelihood of sustaining a TBI (1, 2). In addition, there is a high degree of overlap between the neural circuitry mediating addictive behaviors (3) and brain regions most frequently implicated in physical head trauma (4, 5), with both chronic alcohol exposure and TBI preferentially affecting the integrity of prefrontal and limbic circuitry. The combination of commonly affected neuronal circuitry and high comorbidity provides a strong rationale for the potentially negative synergistic effects of chronic heavy drinking and head trauma on underlying neuronal circuitry. However, the consequences of TBI on maladaptive drinking behaviors in individuals with alcohol use disorders (AUD) are relatively unknown (6).

Abnormal functional organization of prefrontal and limbic circuitry is thought to underlie the enhanced salience of drug-related cues within reward circuitry in the addicted brain, while simultaneously weakening the strength of cognitive control (7). The prefrontal cortex and limbic structures are frequently implicated in compulsive drug seeking, craving and self-administration due in part to the high concentration of dopamine receptors in these areas (for reviews see 3, 8). In humans, visual, olfactory and gustatory alcohol-related cues elicit increased responses in nucleus accumbens (NAc), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), hippocampus, ventral tegmental area (VTA), cerebellum, and anterior insula compared to neutral non-alcohol related cues in AUD (9–13). Increased activation within several of these structures correlates with greater levels of AUD severity (12) and shows a reduced response following alcohol-related treatment (e.g., 14, 15). These results suggest that stronger engagement within this reward circuitry is elicited by alcohol-related cues as AUD severity (e.g. addictive behavior, loss of control, years drinking) worsens. Finally, tissue atrophy occurs within many of these same structures at a much faster rate in AUD relative to normal aging (16, 17). However, gray matter atrophy has been found across several psychiatric diagnoses (18), suggesting that it may not be unique to AUD.

Head trauma, whether experienced prior to the initiation or following excessive alcohol use, has the potential to further damage prefrontal/limbic circuitry mediating addictive behaviors.

TBI preferentially affects these regions due to both skull morphology (i.e., bony protuberances) and the accumulation of shear stress in deep midline regions following external mechanical forces, resulting in both lesions and increased atrophy within these regions (4, 5). Critically, the secondary injury pathways associated with chronic AUD and TBI are also similar. Diffuse axonal injury represents the most common pathology across the spectrum of TBI (19) and long-term exposure to heavy alcohol use results in axonal degeneration (20, 21). Neuroinflammation represents another comorbid pathology of AUD (22) and TBI (23), with both AUD and TBI also involving a complex secondary neurometabolic crisis/oxidative stress that occurs over a prolonged period of time (20, 24).

Thus, it is possible that comorbid histories of chronic alcohol use and head trauma affect key prefrontal/limbic circuitry in a synergistic fashion. Emerging preclinical (25, 26) and clinical (27, 28) evidence suggest that TBI may increase addictive behaviors in a causal manner. Although contrary evidence exists (29, 30), the majority of previous studies suggest more negative neurocognitive and clinical outcomes (e.g., longer hospital stays, higher mortality) in TBI patients with histories of excessive alcohol use relative to those without (31–33). The few imaging studies that have been conducted to date suggest increased structural abnormalities in white matter (31) and general atrophy (33) in TBI patients with a history of severe drinking relative to TBI alone. In contrast, to our knowledge no studies to date have investigated the combined effects of AUD and TBI on brain function, or compared brain structure/function changes relative to AUD alone to more carefully isolate these confounding factors.

The present study therefore examined functional activation for gustatory alcohol cues (i.e., each individual's favorite alcoholic drink) relative to a highly appetitive control cue (lychee juice). Based on previous literature showing a positive relationship between severity and activation (12, 14, 15), we predicted that a combined history of AUD and TBI would result in increased functional response for alcohol relative to appetitive control in prefrontal/limbic circuitry relative to AUD alone. We also predicted that these same ventrolateral and ventral medial prefrontal and limbic structures would show increased evidence of atrophy along with the cerebellum in individuals with AUD and TBI compared to AUD alone.

Methods and Materials

Data from a total of 152 participants (103 males; mean age = 39.08 ± 8.83 years old) were included in the current study. These data were collected as part of a parent study examining the effects of Olanzapine on reducing alcohol consumption (12, 34). However, data presented in the current manuscript were collected at baseline and prior to initiation of the clinical trial. Participants were between the ages of 21 and 55 with a recent history of heavy alcohol use (greater than 21 [men] or 14 [women] drinks per week for four consecutive weeks in the past 3 months), a desire to decrease alcohol consumption, and who had completed a modified version of the Rivermead Post-Concussion Symptoms Questionnaire (RPSQ; 35, 36). Available structural imaging data was limited to 109/152 participants, with an additional 3 participants discarded due to poor data quality (structural data final n: AUD +TBI = 62; AUD alone = 44). Out of the remaining participants, 99 had available structural and functional data on an alcohol cue reactivity task (12), with 7 further identified as motion

outliers (greater than 1.0 mm average framewise displacement). Thus, the final dataset for the cue reactivity task consisted of 55 AUD+TBI and 37 AUD.

Participants with prior history of neurological disorder, severe neurological abnormality on structural imaging, major psychiatric disorders (herein defined as any psychotic disorder, bipolar disorder or major depression with active suicidal ideation), severe TBI (loss of consciousness > 12 hours) or pregnancy were excluded. Current poly-substance use was ruled out with a combination of structured interview (see below) and urine screens. On the day of assessment, all participants had a breath alcohol concentration of 0.0 and were not in acute withdrawal (score greater than 8 on the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised) and had a negative drug screen with the exception of marijuana. The University of New Mexico Human Research Review Committee approved this study and all participants provided written informed consent prior to study enrollment.

Clinical Evaluation

See Supplemental Materials for full details. Past and current diagnosis of Alcohol/Drug Abuse or Dependence was derived from the Structured Clinical Interview for DSM-IV-TR (SCID). Lifetime history of TBI exposure (primary independent variable) was determined via a standardized, semi-structured interview based on the RPSQ. As part of the TBI interview, each participant rated cognitive and somatic symptoms associated with up to 4 separate TBIs, as well as the resolution of these symptoms. Data was also collected on age of injury, whether the injury involved a loss of consciousness or post-traumatic amnesia (mild injury = loss of consciousness 30 minutes and post-traumatic amnesia 24 hours), and whether the injury occurred under the influence of alcohol or other substances. Additional clinical measures included the Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), and the Impulsive Sensation Seeking Scale (ImpSS).

Recent drinking history was assessed with the Timeline Followback interview (TLFB) with memory cues to assess the quantity and frequency of daily drinking, as well as cigarette and marijuana use within the last 60 days. Participants also completed the Drinking History Questionnaire (DHQ), the Alcohol Use Disorders Identification Test (AUDIT), the Pennsylvania Alcohol Craving Scale (PACS), and the Impaired Control Scale (ICS). Several extreme outliers existed for self-reported quit attempts (range 0 to 400). This data therefore underwent a 90% (< 5% and > 95%) winsorization prior to analyses.

Task

The task used in the current study was identical to previous publications (12) and thus details are only briefly presented. Participants were exposed to either gustatory alcohol cues (i.e., each individual's favorite alcoholic drink) relative to a highly appetitive control cue (lychee juice). The gustatory stimuli were delivered to participants via Teflon tubing using a computer-controlled gustometer. Each trial began with the word 'Ready' on the screen for 2 s, followed by taste cue presentation for 24 s, during which participants were instructed to Taste Alcohol (or Juice; 1–10 s and 12–22 s) and Swallow (10–12 s, 22–24 s). Each taste cue presentation was followed by a 16 second washout period during which the word 'REST' appeared on the screen. After this washout period, participants were asked to rate their

current urge to drink alcohol. There were six alcohol and six control trials (12 trials total) arranged pseudorandomly across two separate runs.

Imaging Data Acquisition

All imaging data were collected on a Siemens 3 Tesla Tim Trio system using a 12 channel head coil. Paper tape was placed across participants' foreheads to reduce motion. Structural images were collected with magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo (MPRAGE) sequence [TEs (echo time) = 1.64, 3.5, 5.36, 7.22, and 9.08 ms; TR (repetition time) = 2.53 s; flip angle = 7°; NEX (number of excitations) = 1; slice thickness = 1 mm; FOV (field of view) = 256 mm; and resolution = 256 × 256]. Functional images were collected with a single-shot, gradient-echo echoplanar pulse sequence [TE = 29 ms; TR = 2000 ms; flip angle = 75°; FOV = 240 mm; voxel size: 3.75 × 3.75 × 4.55 mm³].

T₁ Structural Data Analyses

The FreeSurfer reconstruction pipeline (version 5.3) was used to generate cortical thickness values and regions of interest (ROI) based on standard labels for *a priori* cortical and sub-cortical structures. Individual subject segmentation results were visually inspected for quality assurance purposes and corrected when necessary. Cortical thickness maps were projected to surface-based vertices, smoothed with 10 mm full width at half maximum Gaussian kernel and compared across AUD+TBI versus AUD groups. Results were corrected for multiple comparisons at $p < 0.05$ (vertex-wise = 0.001 and cluster-wise) using Monte Carlo simulations in the FreeSurfer package. *A priori* analyses focused on ventromedial, lateral prefrontal cortex, hippocampi, thalami, basal ganglia (caudate, globus pallidus and putamen) and cerebellum. All volumes were normalized by FreeSurfer estimated total intracranial volume (ETIV) to control for overall brain size prior to analyses. Results were Bonferroni corrected at $p = 0.01$ to control for multiple comparisons. Secondary volumetric analyses evaluated the potential effects of comorbid AUD+TBI on overall white and grey matter volumes.

fMRI Image Analyses

Functional analyses were completed using the FMRIB Software Library (FSL) software package and are similar to our previous publications (13, 37). The first 3 volumes of each run were discarded due to T₁ equilibrium effects. A rigid body motion correction was then used to align all images to the first image using FMRIB's Linear Image Registration Tool. Non-brain tissue removal on the time-series was conducted using FSL's Brain Extraction Tool. Data were then spatially smoothed with a 6 mm full-width half-max Gaussian kernel, temporally filtered using a high-pass filter of 90 sec, and grand mean intensity normalized. Regressors of interest (alcohol and juice cues, baseline for alcohol and juice, and urge ratings for alcohol and juice) were first formed by convolving the design matrix with a double gamma hemodynamic response function. Consistent with prior modeling of this task (13, 37), the primary contrast of interest compared parameter estimates for the presentation of the alcohol cue and the presentation of the juice cue. Individual runs were first combined within subjects using a fixed effects model, with time-series analyses conducted using FMRIB Improved Linear Model with local autocorrelation estimation. The alcohol versus juice contrast map was registered to the Montreal Neurological Institute (MNI) 152-brain

template by combining two separate transformations for native (native echo-planar image to native T₁-weighted image) and template (native T₁- to standard T₁-weighted images) space. FLIRT was used for the initial linear registration, and was adjusted using FMRIB's Nonlinear Image Registration Tool.

Voxel-wise results were corrected for false positives at $p < 0.05$ based on 10,000 Monte-Carlo simulations in AFNI's 3dClustsim using spherical autocorrelation ($p < 0.001$ and minimum cluster size = 1112 microliters).

Results

Clinical Results

Results indicated that 90/152 participants who completed the modified RPSQ reported sustaining at least one mild to moderate TBI. A total of 64/90 reported sustaining a single TBI, 18/90 reported experiencing two TBIs, 6/90 reported three TBIs, and 2/90 participants reported four or more TBIs. Of the participants reporting a TBI, seven had insufficient self-report data with which to classify the TBI as mild or moderate in severity. Out of the 83 remaining, 73 (88.0%) met clear diagnostic criteria for mild TBI.

The main goal of the demographic and clinical tests was to determine if the AUD+TBI and AUD groups were statistically equivalent (i.e., confirm null hypothesis) on clinical variables. As such, all tests were performed without correction for multiple comparisons to provide as liberal a threshold as possible. Comparison of key demographic/clinical data (see Table 1 for all p -values and effect sizes) for each of the three samples (clinical, structural analysis and functional analysis datasets) indicated no significant differences on sex distribution, age, levels of education, anxiety (BAI), age of drinking onset or years of regular drinking (DHQ), or impulsive sensation seeking behavior (ImpSS) between AUD+TBI and AUD alone.

Similarly, there were no group differences in maximum reported number of drinks in an episode, percent of days drinking, or the number of patients that smoked marijuana or cigarettes on at least one day covered by the TLFB. The only significant group difference found in the clinical data was seen in the structural sample for number of quit attempts ($p = .042$; uncorrected), with the AUD+TBI group having attempted more than the AUD group (see Table 1). A trend group difference on measures of alcohol consumption and related problems (AUDIT) was seen across all samples (full: $p = .084$; structural: $p = .053$; functional: $p = .077$; uncorrected). Depending on the sample, other uncorrected trend group differences were observed on measures of alcohol craving (PACS; full sample, $p = .060$), failure to control drinking behavior (ICS; full sample, $p = .050$), and depression (BDI-II; functional: $p = .067$), as well as on average drinks per drinking day as reported on the TLFB (functional: $p = .066$; uncorrected).

Cortical Thickness and Volumetric Results

Results from the cortical thickness analyses indicated no significant differences in *a priori* (ventromedial or lateral prefrontal cortex) or other cortical regions between AUD+TBI relative to AUD alone following appropriate corrections for false positives. A cortical representation of effect sizes (Cohen's d) indicated small to moderate effects of group

across all cortical regions (Figure 1). There were no significant differences in ETIV between groups ($p > 0.10$). A series of ANCOVAs indicated no groupwise differences in hippocampi, basal ganglia, thalami or cerebellar volumes following false positive correction, with all effect sizes in the small range (all p 's > 0.10 ; Cohen's d range: $-0.22 - 0.09$). Secondary analyses were also not significant for the main effect of group (both p 's > 0.10) for overall grey (Cohen's $d = -0.07$) or white matter volumes (Cohen's $d = -0.23$).

Cue Reactivity Results

Similar to previous results (12), examination of the contrast of Alcohol $>$ Juice collapsed across group revealed greater response for the alcohol cue in bilateral anterior insula/OFC, anterior cingulate (dorsal, ventral), medial prefrontal cortex (PFC), posterior cingulate cortex, dorsal striatum (caudate and putamen), thalamus, brainstem and cerebellum in both groups (Figure 2A). Comparison of the AUD+TBI and AUD alone groups revealed no significant differences following appropriate correction for false positives, with all voxel-wise effects typically in the small to medium range (Figure 2B).

Supplemental Analyses

Increased AUD severity has been found to be associated with increased brain reactivity to relevant alcohol cues (12) and decreased GM volume throughout temporal, parietal, frontal, and occipital lobes (38). Therefore, similar voxel-wise linear regressions were conducted for both functional and cortical thickness analyses using AUD severity measures (i.e., AUDIT, ICS, average number of drinks per drinking day, and years of regular drinking) as covariates in an attempt to decrease variance and increase the sensitivity of the main group variable (39). However, both secondary analyses for functional and cortical thickness data remained negative. Similarly, repetitive head trauma has also been suggested to be a risk factor for long-term neurological changes relative to single injury (40). Therefore, analyses were repeated with number of injuries treated as a continuous variable; however, these results were also negative.

Discussion

The combination of commonly affected neuronal circuitry (prefrontal and limbic) and high comorbidity provides a strong rationale for the potentially negative synergistic effects of chronic heavy drinking and head trauma on brain structure/function. Current results indicated null findings in terms of observable differences on demographic and clinical measures between patients with AUD+TBI vs AUD alone, suggesting that the groups were well-matched. Specifically, the only significant clinical difference between the groups was found in the structural sample, with the AUD+TBI group having attempted to quit drinking more than the AUD group (uncorrected for multiple comparisons). Although effect sizes were generally in the small range for maladaptive drinking behaviors, most of these behaviors tended to be worse for the AUD+TBI group. Similarly, there were no significant differences in structural integrity or functional activation between AUD+TBI and AUD patients even after controlling for AUD severity, with predominantly small effect sizes observed. Considered collectively, current findings suggest that larger sample sizes than

those employed in the current study may be needed to obtain significant effects regarding combined head trauma and alcohol exposure.

Participants were enrolled into the current study due to a history of heavy alcohol use, with 59.2% also reporting a positive lifetime history of TBI. Similar to recent epidemiological estimates (41), the majority of TBI (88.0%) reported in the current study were mild in nature. Importantly, the overall rate of TBI was approximately 1.6 times the rate of mTBI (36.4%) self-reported elsewhere in the general population (42). This supports previous reports of high comorbidity, with approximately 30–50% of the 1.6 million new mild TBI cases occurring in conjunction with alcohol use (43, 44). However, current results suggest that the addition of a TBI did not further negatively influence maladaptive alcohol use behaviors to a large extent (i.e., small effect sizes consistently across samples). Clinical findings of alcohol use after TBI have been mixed with some finding an increase and others a decrease in use (for a review see 25). This could be a result of variable sampling strategies for factors such as pre-injury alcohol use, post-injury reasons for alcohol use (e.g. physical pain cessation, neurological injury, or comorbid mental illness) as well as TBI severity.

To our knowledge, this is the first study to examine how a combined history of TBI+AUD affects functional activation within the cue reactivity circuitry. Both groups of participants exhibited increased alcohol-cue reactivity in bilateral anterior insula/OFC, anterior cingulate, medial PFC, posterior cingulate cortex, dorsal striatum, thalamus, brainstem and cerebellum relative to a carefully matched appetitive control. These regions are consistent with previous studies using gustatory alcohol-cues (9, 12, 13), as well as a meta-analysis of neuroimaging studies on alcohol-cue reactivity (45). The mesocorticolimbic circuitry ascribes incentive salience or motivation to conditioned stimuli that indicate reward (for recent reviews see 46, 47), including food cues (48, 49). However, alcohol and drugs produce a dopamine response that is both larger in amplitude and longer in duration than other appetitive cues within this circuitry (50, 51), especially for individuals with substance use disorders (3, 8). Even though physical head trauma preferentially affects a similar circuit within prefrontal and limbic regions (4, 5), the combined effects of a history of physical trauma and substance abuse were not large enough to reach conventional levels of statistical significance when correcting for false positives.

Animal data also suggests that atrophy within the limbic circuitry and cerebellum follows a dose-dependent relationship in terms of alcohol consumption (52). Previous studies have also reported increased structural abnormalities in white matter (31) and general atrophy (33) in TBI patients with histories of excessive alcohol use relative to TBI alone. However, the current study did not observe significant differences in cortical thickness, sub-cortical volumes or cerebellar volumes between AUD+TBI relative to AUD alone, with small effect sizes that were generally bi-directional in nature. As increased AUD severity has been associated with decreased GM volume throughout temporal, parietal, frontal and occipital lobes (38), we also repeated all structural and functional analyses controlling for the effects of drinking severity. However, the results from these secondary analyses were also negative.

Discrepancies between previous and current findings are likely a result of our use of a control group that is more carefully matched on lifetime history of alcohol exposure (i.e.,

AUD without a history of head trauma). The two previous studies on structural integrity (31, 33) were also conducted from a TBI perspective (i.e., TBI patients with and without alcohol problems), which under-samples individuals with a history of problematic drinking. The potential importance of patient sampling characteristics are highlighted by secondary analyses in these studies demonstrating greater neurocognitive deficits (53) and a higher number of white matter abnormalities (31) in TBI participants with more significant histories of alcohol use.

It is widely recognized that there is substantial heterogeneity in biological and psychosocial mechanisms that underlie the development of AUD (54) as well as heterogeneity and “chaos” inherently associated with mTBI (55). This heterogeneity in both disease processes may have limited our ability to detect group-wise differences relative to other studies which compare patient samples versus healthy controls. Moreover, it is possible that chronic alcohol use and TBI may interact to accelerate aging. These two conditions have separately been shown to be the largest environmental risk factors for premature cognitive decline and young onset dementia (56–58), and negative synergy may become more apparent in older individuals than studied in the current experiment (21 to 55 years of age).

Several limitations of the study should be noted. First, only self-report data was collected for assessing TBI, AUD and recent drinking history. However, studies have established the reliability of self-report for both drinking history (59) and TBI (60). Moreover, the current study also included more objective outcome measures (imaging data) that are less likely to be influenced by subtle inaccuracies in reporting. Second, although our overall sample size was relatively large, the heterogeneity of each individual disease state may have limited our power to detect the smaller effect sizes suggested by current data. Third, TBI can possibly be both a cause and a consequence of AUD (61), and the current sample did not have enough information (i.e., exact date of onset) to resolve these discrepancies. Fourth, patients with severe TBI were intentionally eliminated from the study, which may limit the generalizability of current null findings to a more mild to moderate injury group. However, mTBI accounts for approximately 80–85% of all TBI (41), and atrophy/poor outcomes are expected for the vast majority (~ 95%) of severe TBI patients. Nonetheless, future studies should examine the influence of more moderate and severe TBI on outcomes in alcohol research. Finally, previous research (32, 33) has indicated a synergistic effect from combined AUD+TBI on other domains, such as cognition, which were not investigated in the current study.

In summary, the current study did not find significant evidence of synergistic effects from combined physical trauma and chronic alcohol exposure on maladaptive drinking behaviors, brain function during cue reactivity or on brain structure relative to a carefully matched group of AUD without a self-reported history of head trauma. These null findings remained even when controlling for AUD severity and the self-reported total number of injuries. Collectively, these results suggest that a single mTBI was not sufficient to alter drinking behaviors and/or underlying neurocircuitry at detectable levels, and that previous cross-sectional alcohol-based comparison of drinkers of similar severity are not severely compromised by single mTBI effects. Future work may benefit from examining this

combined disease state in larger samples, try to differentiate the two pathological processes relative to healthy controls or examine more long-term effects of combined injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Cortical Thickness (Cohen's d)

Figure 1.

Figure 1 depicts Cohen's d effect size maps of cortical thickness in the right (R) and left (L) hemispheres for participants with a comorbid history of alcohol use disorders and traumatic brain injury (AUD+TBI) and alcohol use disorders (AUD) alone. Small effect sizes ($d > |0.3|$) appear in red (AUD+TBI > AUD) or blue (AUD > AUD+TBI), depending on the direction of the effect. Medium effect sizes ($d > |0.6|$) appear in yellow (AUD+TBI > AUD) or cyan (AUD > AUD+TBI).

Figure 2.

Panel A displays brain areas showing significantly different activation between alcohol (ETOH) and lychee juice taste trials during the cue reactivity task collapsed across both groups. Regions exhibiting increased effect for ETOH are represented in warm colors (red: $p < 0.001$ yellow: $p < 0.0001$) following correction for false positives. Panel B presents Cohen's d effect sizes for the ETOH minus juice contrast between participants with a comorbid history of alcohol use disorders and traumatic brain injury (AUD+TBI) relative to alcohol use disorders (AUD) only. Regions with effect sizes for AUD+TBI relative to AUD greater than 0.3 (small) are shown in red while those regions greater than 0.6 (medium) are shown in yellow. No voxels exhibited greater effect sizes for the AUD alone group. Select axial (Z) slices in both Panels are displayed at 4 mm intervals according to the MNI atlas with the right (R) and left (L) hemispheres denoted.

Table 1

Summary of participant demographic and clinical measures.

			AUD			AUD+TBI				
			<i>N</i>	<i>Mean</i>	<i>SD</i>	<i>N</i>	<i>Mean</i>	<i>SD</i>	<i>p-value</i>	<i>Cohen's D</i>
Demographics										
<i>Sex</i>	<i>CS</i>	44M, 18F				59M, 31F			.483	
	<i>SS</i>	29M, 15F				40M, 22F			.882	
	<i>FS</i>	24M, 13F				35M, 20F			.904	
<i>Age (years)</i>	<i>CS</i>	62	37.94	8.30		90	39.87	9.13	.186	0.22
	<i>SS</i>	44	38.66	8.35		62	39.92	8.66	.455	0.15
	<i>FS</i>	37	38.59	8.68		55	40.11	8.90	.421	0.17
<i>Education Level</i>	<i>CS</i>	62	13.68	2.44		88	13.10	1.99	.115	-0.26
	<i>SS</i>	44	13.82	2.64		60	13.05	1.86	.103	-0.34
	<i>FS</i>	37	13.89	2.83		53	13.04	1.87	.113	-0.36
Clinical Measures										
<i>BAI</i>	<i>CS</i>	61	10.44	10.34		88	9.64	7.99	.592	-0.09
	<i>SS</i>	43	10.02	10.79		60	9.48	8.22	.774	-0.06
	<i>FS</i>	37	9.78	10.96		54	9.39	8.41	.846	-0.04
<i>BDI-II</i>	<i>CS</i>	60	15.15	9.29		85	17.71	11.11	.147	0.25
	<i>SS</i>	44	15.45	9.83		58	18.59	10.38	.126	0.31
	<i>FS</i>	37	14.76	9.64		51	18.92	10.93	.067	0.40
<i>ImpSS</i>	<i>CS</i>	61	8.30	4.56		89	8.39	4.98	.903	0.02
	<i>SS</i>	43	8.28	4.89		61	8.69	5.10	.683	0.08
	<i>FS</i>	37	8.68	4.93		54	9.06	5.16	.726	0.08
ETOH/SA Measures										
<i>ICS</i>	<i>CS</i>	62	28.35	7.14		88	30.52	6.24	.050	0.32
	<i>SS</i>	44	28.57	7.40		60	30.65	6.38	.128	0.30

	AUD			AUD+TBI			<i>p-value</i>	<i>Cohen's D</i>
	<i>N</i>	<i>Mean</i>	<i>SD</i>	<i>N</i>	<i>Mean</i>	<i>SD</i>		
	<i>FS</i>	37	28.81	7.46	53	30.92	6.42	.154
<i>PACS</i>	<i>CS</i>	62	15.39	7.75	89	17.64	6.20	.060
	<i>SS</i>	44	16.02	7.90	61	17.15	6.07	.431
	<i>FS</i>	37	16.03	7.78	54	17.30	6.03	.407
<i>AUDIT</i>	<i>CS</i>	61	22.84	7.16	88	24.81	6.56	.084
	<i>SS</i>	44	22.57	7.41	60	25.33	6.90	.053
	<i>FS</i>	37	22.68	7.63	54	25.44	6.99	.077
<i>DHQ</i>								
-Age of Drinking Onset	<i>CS</i>	62	13.74	3.03	88	13.47	3.01	.582
	<i>SS</i>	44	13.84	2.80	60	13.58	2.97	.656
	<i>FS</i>	37	13.81	2.76	53	13.75	2.95	.928
-Years Regular	<i>CS</i>	62	20.11	5.52	89	19.36	5.97	.433
	<i>SS</i>	44	19.86	4.72	61	20.16	6.81	.802
	<i>FS</i>	37	19.76	4.69	54	20.56	7.12	.551
-Quit Attempts	<i>CS</i>	60	6.23	7.56	87	8.74	10.09	.105
	<i>SS</i>	43	5.90	8.31	59	10.34	13.35	.042
	<i>FS</i>	36	5.88	8.20	52	9.39	12.28	.111
<i>TLFB</i>								
-Average # Drinks Per Drinking Day	<i>CS</i>	62	8.58	4.10	89	9.45	4.67	.235
	<i>SS</i>	44	8.33	4.28	61	9.44	4.45	.203
	<i>FS</i>	37	7.86	4.23	54	9.62	4.55	.066
-Max # Drinks in an Episode	<i>CS</i>	62	15.24	7.08	89	17.14	8.42	.148
	<i>SS</i>	44	15.25	7.69	61	17.33	8.01	.186
	<i>FS</i>	37	14.56	7.82	54	17.23	8.24	.124

	AUD			AUD+TBI			<i>p-value</i>	<i>Cohen's D</i>
	<i>N</i>	<i>Mean</i>	<i>SD</i>	<i>N</i>	<i>Mean</i>	<i>SD</i>		
-% Drink Days	<i>CS</i>	73.37	25.93	89	74.59	23.52	.764	0.05
	<i>SS</i>	73.74	25.05	61	70.81	25.07	.556	-0.12
	<i>FS</i>	76.32	25.23	54	71.60	25.59	.387	-0.19
-Smoked Marijuana	<i>CS</i>	47NS, 14S		63NS, 26S			.394	
	<i>SS</i>	36NS, 7S		43NS, 18S			.120	
	<i>FS</i>	31NS, 5S		40NS, 14S			.170	
-Smoked Cigarette	<i>CS</i>	27NS, 34S		40NS, 49S			.934	
	<i>SS</i>	21NS, 22S		29NS, 32S			.896	
	<i>FS</i>	17NS, 19S		27NS, 27S			.796	

Notes: AUD = Alcohol Use Disorder; AUD+TBI = Comorbid History of Alcohol Use Disorder and Traumatic Brain Injury; N = Sample size; SD = Standard deviation; CS = clinical sample; SS = structural sample; FS = functional sample; M = Male; F = Female; Education level was determined based on number of years in school; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; ETOH = Alcohol; SA = Substance Abuse; PACS = Pennsylvania Alcohol Craving Scale; AUDIT = Alcohol Use Disorders Identification Test; ICS = Impaired Control Scale; ImpSS = Impulsive Sensation Seeking scale; DHQ = Drinking History Questionnaire; TLFB = Timeline Followback; NS = Not smoked any days; S = Smoked at least one day.