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Acute Alcohol Intake Alters Resting State Functional Connectivity of Nucleus Accumbens with Pain-related Corticolimbic Structures

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Abstract

Background—The nucleus accumbens (NAc) is a ventral striatal structure underlying reward, reinforcement, and motivation, with extensive anatomic and functional connections to a wide range of affective processing structures (medial prefrontal cortex (mPFC), amygdala, and insula). Characterizing how acute alcohol intake affects resting state functional connectivity (rsFC) between the nucleus accumbens (NAc) and these regions will improve mechanistic understanding of alcohol's neurobehavioral effects, including the neural overlap between acute alcohol effects and pain processing.

Methods—Fifteen healthy social drinkers (10 women; age: 25–45 years) were included in the study. Participants completed one session in which they consumed an alcohol dose targeting a breath alcohol concentration of 0.08 g/dL, and in a second a placebo beverage. Nine-minute resting state fMRI scans were acquired 30–35 minutes after beverage administration during each session. rsFC between NAc and *a priori* corticolimbic regions of interest (mPFC, amygdala, and insula), were compared between beverage conditions. We also conducted an exploratory whole-brain seed-to-voxel analysis of NAc FC.

Results—Alcohol intake reduced rsFC between NAc and mPFC, as well as NAc and amygdala. Alcohol also reduced rsFC between NAc and a 97-voxel cluster including bilateral paracingulate cortex and anterior cingulate cortex.

Conclusions—Findings suggest that acute alcohol intake reduces rsFC between NAc and several structures, including mPFC, amygdala, and rostral ACC in healthy social drinkers. These structures underlie reward, motivated behavior, and emotion regulation, and may provide mechanistic insight to how alcohol affects related processes, including pain.

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Contributors

JB and MR designed the study, JB and BS collected data, JB conducted analyses, and JB, BS, and MR wrote the manuscript. All authors approved the final version of the manuscript for submission.

Conflict of Interest

The authors declare no conflict of interest.

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Keywords

alcohol; resting state; functional connectivity; nucleus accumbens; pain

1. Introduction

The nucleus accumbens (NAc) is a basal forebrain structure with neuroanatomic and functional connections to a range of structures, including medial prefrontal cortex (mPFC), amygdala, and insula (Ikemoto, 2010). The role of the NAc in reinforcement and reward associated with alcohol use is well appreciated (Russo et al., 2010); briefly, alcohol-induced release of dopamine and opioid peptides in the NAc underlie its reinforcing properties (Koob and Volkow, 2010). Chronic pain and alcohol use disorder (AUD) frequently co-occur (e.g., Boissoneault et al., 2019) and involve overlapping neural substrates (Apkarian et al., 2013, Becerra and Borsook, 2008; Egli et al., 2012; Scott et al., 2006; Zale et al., 2015), but empirical studies regarding alcohol effects on resting state functional connectivity (rsFC) between regions and networks relevant to alcohol/pain interactions, including NAc, are lacking.

Previous studies have examined changes in rsFC with acute alcohol administration (e.g., Gorka et al., 2018; Shokri-Kojori et al., 2017). However, acute alcohol effects on NAc-related circuits underlying motivation/reward, pain processing and chronification have not previously been examined. Thus, this study examined the acute effects of alcohol on rsFC between NAc and mPFC. Because alcohol can have analgesic effects in experimental settings (Thompson et al., 2017), and chronic pain is associated with greater rsFC between these structures, we hypothesized that acute alcohol intake would reduce NAc-mPFC connectivity. We also examined alcohol effects on connectivity of NAc with amygdala and insula, given their extensive anatomic and functional connections to the NAc (Ikemoto, 2010) and their role in modulating both alcohol's reinforcing effects and the pain experience (Koob and Volkow, 2010).

2. Materials and Methods

2.1 Participants

Community-dwelling healthy drinkers (N=15; 10 women), 25–45 years of age, were recruited as part of a study regarding biopsychosocial mechanisms underlying alcohol analgesia. Informed consent was obtained prior to data collection. The study was approved by the University of Florida IRB (Protocol #2018–0889).

2.2 Screening Procedure

During the screening/eligibility session, participants completed questionnaires (demographics; medical history; Beck Depression Inventory-II (BDI-II; Beck et al., 1996); State-Trait Anxiety Inventory (STAI; Spielberger, 1986); Alcohol Use Questionnaire (AUQ; Cahalan, 1969); and the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993). Exclusionary criteria: consuming <1 beverage containing alcohol/month during the prior 6 months; history of chronic pain; regular use of analgesic medications; psychotic

disorders; under-controlled hypertension or diabetes; neurological disease; serious medical illness; and lifetime smoking >100 cigarettes. Individuals indicating impaired cognitive function, history of drug or alcohol dependence, problematic alcohol use (AUDIT 8), significant depression (ie, BDI-II >20), or being alcohol naïve. Prescription and over-the-counter (OTC) medication use was allowed, provided they did not contraindicate alcohol intake.

2.3 Laboratory Sessions

Participants were scheduled for two laboratory sessions separated by at least 48 hours. Participants fasted for 4 hours and abstained from consuming alcohol 24 hours before sessions (Boissoneault et al., 2014; Lewis et al., 2013). Normal medications were permitted, but not allergy medications or analgesics. Prior to beverage administration, participants provided a urine sample for drug (tetrahydrocannabinol, cocaine, benzodiazepines, morphine, and methamphetamine) and pregnancy testing. A baseline breath alcohol concentration (BrAC) measure was also taken. Positive results were exclusionary. Participants consumed a ~220 kcal breakfast one hour before alcohol administration.

2.4 Alcohol Administration

Participants completed two laboratory sessions in counterbalanced order in which they were administered a placebo (0.00 g/dL target BrAC) or alcohol (0.08 g/dL target BrAC) on a blinded fashion. For alcohol sessions, the quantity of 95% medical-grade ethanol needed to achieve a BrAC of 0.08 g/dL (Watson et al., 1981) was mixed with sugar-free lemon-lime soda in a 1:3 ratio and split into two servings (Boissoneault et al., 2014; Harrison et al., 2007). Placebos contained only soda. Drinks were misted with ethanol, and a small amount of ethanol was placed on the surface and rim of placebo beverages. Participants consumed both servings within 5 minutes and then rinsed their mouths with water. Placebo efficacy was assessed at the end of sessions by asking participants if they believed their beverage contained alcohol.

2.5 Breath and Saliva Alcohol Concentration

BrAC was obtained every 10 minutes after alcohol consumption using a standard breathalyzer (CMI, Inc., Owensboro, KY, USA). In the scanner, salivary alcohol concentration (SAC) was assessed between acquisitions using QED A150 tests (OraSure Technologies, Inc., Bethlehem, PA, USA), which correspond closely to BrAC (Bates and Martin, 1996). Participants were transported home when their BrAC was 0.02 g/dL (Brown et al., 2014).

2.6 Imaging Data Acquisition

Twenty-five to thirty minutes after beverage administration, into a Siemens Prisma 3T scanner with a 64-channel head coil. ~30–35 minutes after beverage administration, participants completed a 9-minute eyes-open resting state functional scan with parameters: field-of-view (FOV)=240 mm, voxel-wise resolution=2.5×2.5×2.5mm, 51 axial slices, inter-slice gap=0, acceleration factor=3, and TR/TE/FA=1500ms/30ms/70°. Participants were

instructed to keep their gaze on a fixation cross, let their thoughts wander, stay as still as possible, and to stay awake.

A three-dimensional T1-weighted MP-RAGE whole-brain structural image was also acquired, with parameters: FOV=256 mm, voxel-wise resolution=0.8×0.8×0.8mm, 320 contiguous sagittal slices, acceleration factor=2, and TR/TE/FA=2000ms/2.99ms/8°.

2.7 Image Processing and Analysis

SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) and the CONN toolbox v18b (Whitfield-Gabrieli and Nieto-Castanon, 2012) were used for fMRI preprocessing. Steps included slice-time correction, realignment, registration, normalization to MNI space, spatial smoothing (8mm FWHM kernel), and motion and signal artifact reduction using the Artifact Detection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect). Volumes where change in mean global signal exceeded 3 standard deviations, translation exceeded 0.5 mm, or rotation exceeded 0.02 rad from the previous image were considered outliers (Chai et al., 2014). Component-based noise correction for physiological and other noise source reduction (Behzadi et al., 2007), as implemented in the CONN toolbox, was applied during first-level processing. Regression was used to reduce the influence of 5 principal components each from signal within CSF and deep cerebral white matter, all six movement parameters and their first-order derivatives, and ART-designated outlier volumes. Maximum composite head motion did not differ significantly between alcohol and placebo sessions ($T_{14}=0.38$, $p=.71$). Average composite head motion ($T_{14}=2.12$, $p=.052$) and the number of detected outlier volumes ($T_{14}=2.00$, $p=.065$) tended to be greater in the alcohol than placebo condition. The mean percentage of outliers was 3.2% in alcohol sessions (range: 0–16.1%) and 1.1% in placebo sessions (range: 0–8.3%).

2.8 Functional Connectivity Analysis

First-level analyses were conducted to determine the BOLD signal correlation between *a priori* ROIs: NAc-mPFC, NAc-amygdala, and NAc-insula. Correlation coefficients were then Z-transformed. For comparability of results with previous studies of NAc-mPFC connectivity, we defined these ROIs as 10mm spheres centered at 10, 12, –8 and 2, 52, –2 (Baliki et al., 2012; Sevel et al., 2019; Woo et al., 2015). Because we did not have hemisphere-specific hypotheses, bilateral amygdala and insula, defined using CONN's Harvard-Oxford cortical and subcortical atlas implementation (Desikan et al., 2006), were averaged. Within-subjects t-tests were used to compare ROI-ROI rsFC between alcohol and placebo. A false discovery rate (FDR) correction ($p<.05$) was implemented to control family-wise error (Benjamini and Hochberg, 1995).

Correlations between the NAc seed and each brain voxel were also calculated for exploratory whole-brain seed-to-voxel analyses. A within-subject t-test characterized the effect of alcohol on whole-brain NAc rsFC vs. placebo. The cluster-forming threshold was $p<.001$. Cluster-wise FDR correction was applied ($p_{FDR}<.05$).

3. Results

3.1 Participant Characteristics

Participants averaged 30.8 years of age ($SD=3.7$) and 20.1 years of education ($SD=2.87$). Mean BDI-II and STAI-trait scores were 3.27 ($SD=3.8$) and 29.3 ($SD=7.4$), indicating minimal distress. Participants consumed, on average, 0.63 ($SD=.37$) oz. absolute ethanol/day over the 6 months prior to screening (~1 standard drink). Maximum single-day consumption during this period averaged 4.68 ($SD=2.05$) oz. absolute ethanol (~8 standard drinks). The mean AUDIT score was 5.1 ($SD = 1.8$).

3.2 BrAC and SAC Measures

Mean BrAC immediately prior to placing participants in the MRI scanner was .066 g/dL ($SD=.017$). SAC measures taken ~6 minutes after the resting state fMRI scan averaged .078 g/dL ($SD=.018$).

3.3 Placebo Efficacy and Impact on rsFC

46.7% (7/15 participants) believed they had received alcohol during the placebo session. Independent t-tests indicated placebo efficacy did not significantly affect rsFC between ROIs ($t_{13}<1.4$, $p>.18$).

3.4 Effects of Alcohol vs. Placebo on NAc rsFC

Consistent with hypotheses, alcohol administration significantly reduced rsFC between NAc and mPFC ($p_{FDR} = .026$), as well as NAc and bilateral amygdala ($p_{FDR} = .017$). However, no effects on NAc and bilateral insula were noted ($p_{FDR} = .87$). Detailed results are presented in Table 1 and Supplemental Figures 1–3.

Whole-brain seed-to-voxel analyses identified a 97-voxel cluster including the bilateral paracingulate and anterior cingulate cortices (ACC) where rsFC with NAc was significantly lower in the alcohol condition ($p_{FDR} = .01$; Figure 1). Detailed results are presented in Table 2 and Supplemental Figure 4.

4. Discussion

Results supported hypotheses that acute alcohol would disrupt NAc-mPFC and NAc-amygdala rsFC. Whole-brain analyses also indicated alcohol-related disruption of NAc-paracingulate/ACC rsFC. Alcohol did not appear to meaningfully affect NAc-insula rsFC.

Alcohol-related reductions in NAc-mPFC connectivity are intriguing given evidence that greater rsFC between these structures is associated with poorer self-regulation of experimental pain (Woo et al., 2015), chronic pain status (Baliki et al., 2010), and development of chronic low back pain (Baliki et al., 2012). In addition, reductions in NAc-mPFC rsFC were noted in a recent study demonstrating improvements in pain modulatory capacity after repeated exposures to delayed onset muscle soreness (Sevel et al., 2019). Thus, the noted alcohol-related reduction in NAc-mPFC rsFC suggests a potential mechanism by which alcohol may influence pain. The directionality of this effect was

opposite of acute methamphetamine (Weafer et al., 2019), suggesting that drugs of abuse likely differ in their effects on corticolimbic rsFC.

Alcohol also reduced NAc-amygdala rsFC. The amygdala contributes to the reinforcing properties of alcohol and the emotional components of pain (Neugebauer et al., 2004), and both chronic pain and AUD are associated with persistent alterations in amygdala function (e.g., Shen et al., 2010; for review, see Egli et al., 2012). Finally, whole-brain analysis indicated alcohol-related reductions in rsFC between NAc and a cluster encompassing paracingulate gyrus and rostral ACC (Brodmann Area 32). This area subserves affective processes; thus, reduced FC with NAc under alcohol likely reflects disruption of a circuit underlying emotional regulation and motivation (Bush et al., 2000). Indeed, NAc-ACC FC has been previously implicated in processing of monetary reward and loss (Crane et al., 2017). Previous studies have linked activity proximal to this cluster to pain processing (Salomons et al., 2004) and empathy (Weissman-Fogel et al., 2011).

4.1 Study Strengths and Limitations

Study strengths include a within-subjects design and *a priori* designation of ROIs with specific relevance to alcohol/pain interactions. Certain limitations also bear consideration. This was an initial analysis of resting state data from an ongoing study. The sample provided sufficient power to detect hypothesized alcohol effects on NAc-mPFC and NAc-amygdala rsFC. Conversely, alcohol's effect on NAc-insula rsFC was trivial ($d_z=.06$) and an infeasibly large sample would be needed to detect it ($N>1700$). However, the limited sample restricted characterization of potential moderators of alcohol effects on rsFC, including chronic heavy drinking, chronic pain, sex, and family history of alcoholism). Although selected to improve comparability with previous studies, the NAc ROI mask used in the study was large (10mm radius) and may have included surrounding tissue. To address this concern, we re-examined the effects of alcohol on rsFC between *a priori* designated ROIs using a 6mm radius NAc mask and found similar results. Finally, although a urine drug screen was used to detect recent use of substances that may confound results or compromise safety, we did not assess typical use of substances besides alcohol.

4.2 Conclusions

Alcohol may reduce rsFC between NAc and structures underlying reward, motivated behavior, and pain processing. Further studies are needed to determine relevance of these effects to alcohol analgesia (Horn-Hoffman et al., 2015; Thompson et al., 2017), pain self-medication behaviors (Riley and King, 2009), and shared risk between chronic pain and AUD (Ditre et al., 2019).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Growing evidence suggests common neural underpinnings of pain and alcohol effects
- Alcohol intake reduced functional connectivity between mesocorticolimbic regions
- Collectively, these regions underlie reward, motivated behavior, and pain response

Figure 1. Left medial view showing the location and spatial extent of a cluster (coordinates: $-2, 42, -4$) including bilateral paracingulate and anterior cingulate cortices where connectivity with NAc was significantly lower in the alcohol vs. placebo condition.

Table 1.Effects of Alcohol Administration on Resting State NAc Connectivity with *a priori* ROIs

Target	Alcohol (SD)	Placebo (SD)	<i>t</i> (df)	<i>p</i> FDR	Cohen's <i>d</i> _z
mPFC	0.22 (0.15)	0.30 (0.15)	2.72 (14)	0.026	0.67
Amygdala	0.12 (0.08)	0.17 (0.11)	3.28 (14)	0.017	0.84
Insula	0.14 (0.17)	0.13 (0.15)	0.17 (14)	0.87	0.06

Table 2.

Results of whole-brain seed-to-voxel analysis of the effect of alcohol on NAc connectivity

Cluster Coordinates	Cluster Size	Cluster Regions	Voxels in Region	% Coverage	pFDR	Alcohol Connectivity (SD)	Placebo Connectivity (SD)	Cohen's dz
-2, 42, -4	97	Left paracingulate cortex	39	3	0.01	0.16 (0.12)	0.30 (0.13)	1.21
		Anterior cingulate cortex	27	1				
		Right paracingulate cortex	13	1				
		Not assigned or less than 1% coverage	18	n/a				