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Article

Preliminary Evidence for Disrupted Nucleus Accumbens Reactivity and Connectivity to Reward in Binge Drinkers

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Abstract

Aims: Dysfunctional brain reward circuitry, particularly in the nucleus accumbens (NAcc), has been proposed as a risk factor for alcohol use disorder (AUD). This risk factor may be evident in binge drinkers (BD), who are at high risk for developing AUD. We examined whole-brain and NAcc reactivity to reward in BD compared to non-binge drinkers (NBD), hypothesizing that groups would differ in their neural reactivity and connectivity.

Methods: Healthy BD (N = 27) and NBD (N = 23)—none meeting AUD criteria—completed a reward-guessing game, the 'Doors' task, during functional magnetic resonance imaging. We conducted an exploratory whole-brain search for group differences, but given our *a priori* hypotheses, we also extracted activation from the NAcc to examine reactivity during reward (Win > Loss) and functional connectivity (FC) to the prefrontal cortex.

Results: Compared to NBD, BD exhibited greater activation in both the right and left NAcc during reward relative to loss. Additionally, NBD drinkers exhibited positive FC between the NAcc and dorsal anterior cingulate (dACC) whereas the BD showed negative FC between these regions. Furthermore, less NAcc–dACC FC was related to more past month alcohol use.

Conclusions: Our results provide preliminary evidence that BD exhibit greater NAcc activation during reward receipt relative to loss. This is consistent with the broader AUD literature and suggests aberrant neural reactivity may precede disorder onset. In addition, BD exhibited less NAcc–dACC FC, perhaps reflecting deficient regulation of activation to rewards compared to losses. This profile of reward brain circuitry could represent neural correlates of vulnerability for AUD.

Short summary: Healthy binge drinkers, at risk for alcohol use disorder, exhibited greater nucleus accumbens activation during reward relative to loss. In addition, binge drinkers exhibited reduced connectivity between the nucleus accumbens and dorsal anterior cingulate, which was associated with more past month alcohol use.

INTRODUCTION

Binge drinking is prevalent in the United States, and is characterized by the intake of large quantities of alcohol (at least 4–5 drinks) in a short period of time (NIAAA, 2004; Courtney and Polich, 2009). Importantly, binge drinking is a risk factor for developing alcohol use disorder (AUD) (Chassin *et al.*, 2002) and is associated with poor psychosocial, cognitive and health outcomes (Jennison, 2004;

Courtney and Polich, 2009; CDC, 2016). Given the substantial burden related to AUD (Rehm *et al.*, 2009; Mokdad *et al.*, 2016), it is critical to better understand the predictors of the disorder, including neural mechanisms associated with binge drinking. Such knowledge will help to target interventions and prevention strategies for those most at-risk of developing AUD.

Brain reward circuitry is implicated in AUD. Notably, alcohol acts in the striatum, including the nucleus accumbens (NAcc) (Volkow *et al.*, 2007; Mitchell *et al.*, 2012), which underlies the rewarding effect of alcohol, the development of incentive salience and drug-seeking behaviors (Koob and Volkow, 2016). Over time, repeated alcohol exposure causes neuroadaptations, dysregulating brain reward circuitry and resulting in compulsive and excessive alcohol use (Koob and Volkow, 2016). Indeed, individuals with AUD differ in their neural responses to reward compared to healthy controls, especially in the NAcc (Koob and Volkow, 2016). Some evidence demonstrates individuals with AUD show increased striatal activation to monetary reward (Bjork *et al.*, 2008b) and alcohol-related cues (Braus *et al.*, 2001; Myrick *et al.*, 2004; Wrase *et al.*, 2002, 2007) compared to healthy controls. However, other studies found no differences in striatal activation to monetary reward outcomes in abstinent individuals with AUD compared to healthy controls (Forbes *et al.*, 2014) or in individuals with a family history of alcoholism (Andrews *et al.*, 2011), indicating the data is mixed. A recent meta-analysis found individuals with substance use disorders (SUD) evidence blunted ventral striatum activation during reward anticipation and enhanced ventral striatum activation during reward outcome (Luijten *et al.*, 2017).

In addition to findings of aberrant NAcc reactivity, evidence suggests dysfunctional connectivity with reward circuitry may contribute to the development of AUD (Sutherland *et al.*, 2012). One study found abstinent individuals with AUD exhibit greater negative functional connectivity than healthy controls between the bilateral NAcc and areas of the prefrontal cortex (medial prefrontal cortex (mPFC), lateral orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (dlPFC)) during monetary reward receipt (Forbes *et al.*, 2014). Additionally, accumulating evidence indicates resting-state connectivity is disrupted between the NAcc and areas of the prefrontal cortex (PFC) (Hong *et al.*, 2009; Ma *et al.*, 2010; Camchong *et al.*, 2013; Cservenka *et al.*, 2014; Wilcox *et al.*, 2011; Motzkin *et al.*, 2014) and structural connectivity is disrupted in reward regions (Squeglia *et al.*, 2015) in at-risk youth and individuals with SUD. Some of these studies show decreased connectivity between the NAcc and the PFC (dorsal anterior cingulate (dACC), frontal operculum and dlPFC) (Hong *et al.*, 2009; Ma *et al.*, 2010; Motzkin *et al.*, 2014; Wilcox *et al.*, 2011), while one study show no group differences (Gu *et al.*, 2010) among individuals with SUD and healthy controls. To date, however, few studies have examined whether neural abnormalities are observed within at-risk individuals.

There is some evidence that disrupted brain reward circuitry predates alcohol use and is a risk factor for alcohol initiation. Adolescents at risk for substance use show hyperactive brain reward circuitry to rewards (Bjork *et al.*, 2010; Ivanov *et al.*, 2012; Stice *et al.*, 2013; Stice and Yokum, 2014). However, the specific reward regions implicated are mixed, as many studies did not look at the NAcc specifically, and other studies fail to detect these effects (Bjork *et al.*, 2008a; Muller *et al.*, 2015). In a combined fMRI and PET study of adolescents examining neural response to monetary reward outcome, at-risk adolescents had similar striatal BOLD response to monetary reward, but demonstrated more dopamine release in the NAcc during monetary reward compared to low risk individuals (Weiland *et al.*, 2017). Further, greater BOLD activation and greater dopamine release in the NAcc were related to experiencing drunkenness at a younger age (Weiland *et al.*, 2017). Together, these data suggest at-risk adolescents exhibit some disruption of NAcc reward circuitry and this disruption may be related to onset and/or chronicity of alcohol use.

Healthy, young adult binge drinkers (BD) offer a unique population to study whether brain reward circuitry is disrupted before the development of AUD. They are at-risk for AUD and for other poor health, psychosocial, and cognitive outcomes (Wechsler *et al.*, 1994; Jennison, 2004). To our knowledge only one other study has examined neural activation to receipt of rewarding outcomes in BD, and this study was in adolescents (Cservenka *et al.*, 2015). As such, the goal of the current study was to understand if reward brain circuitry is disrupted among young adult BD who are at-risk for AUD, but who have not yet developed the disorder. We hypothesized BD would display greater NAcc response and decreased NAcc-prefrontal connectivity to monetary reward relative to non-binge drinkers (NBD), in line with previous SUD studies. Given our *a priori* hypotheses, we first examined whole-brain group differences in activation during reward and then used a region-of-interest (ROI) approach to examine group differences in reactivity to reward within the NAcc. If our results revealed significant group differences in NAcc reactivity, we planned to examine group differences in functional connectivity (FC) between the NAcc and the prefrontal cortex during reward receipt.

METHODS

Design

These data were drawn from a larger study examining relationships between neural reactivity and subjective and objective responses to drugs and alcohol. For the parent study, participants first completed acute drug challenges of d-amphetamine or alcohol—data from these visits were not included in the current study. All participants then attended a separate visit at least a week later for an fMRI scan, during which they completed a reward-guessing game, the 'Doors' task.

Participants

Participants were right-handed, healthy young adults aged 21–31 recruited from nearby college campuses and surrounding communities through online and printed advertisements. Overall, 25 individuals who did not report any binge drinking episodes (i.e. 4+ drinks in a 2-h period for women or 5+ drinks in a 2-h period for men; NIAAA, 2004; Courtney and Polich, 2009) in the last month (NBD) and 29 individuals who reported at least 1 binge drinking episode in the past month (BD) were included. Inclusion criteria included body mass index between 19 and 26, at least a high school education, English fluency, no current or past year DSM-IV diagnosis, no lifetime history of SUD, no serious medical conditions, no night shift work, negative urine drug screen at fMRI visit and no contraindication for fMRI. Participants were excluded if they reported smoking >5 cigarettes per day, daily use of any medications other than birth control, or if they were pregnant, lactating or planning to become pregnant in the next 3 months.

Study procedure

Participants completed an initial screening and orientation visit during which they provided informed consent and completed the Timeline Followback interview (Sobell *et al.*, 1986) to record alcohol use in the past month. Participants were also asked to report the frequency and amount of alcohol use during their period of heaviest drinking. Participants completed drug administration sessions for

the parent study at the University of Chicago (UofC) and then attended a separate fMRI visit at the University of Illinois of Chicago (UIC) 1–2 weeks later. Before the scan participants were screened for MRI safety and provided breath and urine samples to test for recent alcohol and drug use. The Institutional Review Board at UofC and UIC approved the study and written informed consent was obtained. Participants were compensated for their participation.

Reward task and data acquisition

Participants completed a reward-guessing game, the 'Doors' task, during the scan. The Doors task provides an index of reactivity to monetary rewards and losses. Participants were told that behind one of the doors there was a monetary prize of $0.50 ('↑') while behind the other door there was a loss of $0.25 ('↓') and that they should use a button box to choose one of the two doors to either win or lose money for each trial (Supplemental Fig. 1). They were told they had a chance of winning between $0 and $15.00 at the end of the task depending on their performance. However, unbeknownst to participants, the task was rigged, so task behavior had no impact on actual outcomes and therefore was not analyzed or reported. The task consisted of 30 predetermined Wins and 30 Losses presented in a pseudorandom order over two runs. The task lasted for 15-min and is based on a task used in previous studies (Hajcak *et al.*, 2006; Foti and Hajcak, 2009; Carlson *et al.*, 2011) (see Supplement for more information).

Functional MRI data was collected using a 3 T GE magnetic resonance scanner at the UIC Center for Magnetic Resonance Research. Functional images were acquired using a gradient-echo echo-planar images (2 s TR, 25ms TE, 82° flip, 64 × 64 matrix, 200 mm FOV, 3 mm slice thickness, 0 mm gap, with 44 axial slices).

fMRI data analyses

All data were inspected and any individual with >2 mm displacement in any one direction were not included in the analysis resulting in four individuals being excluded (two NBD and two BD) and a total sample size of 50 (23 NBD and 27 BD). Remaining subjects met criteria for high quality and scan stability. There were no significant group differences in peak movements, mean movement, or variability during either run ($P > 0.05$). Preprocessing of fMRI data was conducted using Statistical Parametric Mapping software (SPM12, Wellcome Department of Imaging Neuro-Science, London, UK). Images were spatially realigned, slice-time corrected, warped to Montreal Neurological Institute (MNI) space using the participant's mean functional image, resampled to 2 mm^3 voxels, and smoothed (8 mm^3 kernel). The general linear model was applied to the time series, convolved with the canonical hemodynamic response function and with a 128-s high-pass filter. Condition effects were modeled with event-related regressors representing the occurrence of Win or Loss. Effects were estimated at each voxel, and for each subject. Individual contrast maps for Win trials (>Loss trials) were created for each person. Individual motion parameter files were included in the first levels models as regressors-of-no-interest.

To confirm that the task successfully activated reward-related regions, including the NAcc, during Win > Loss trials, we examined whole-brain task activation across all subjects. Due to concerns of high rates of false positives with lenient significance thresholds and following recent guidelines (Woo *et al.*, 2014; Eklund *et al.*, 2016), neural activity from task effects was considered significant if it exceeded correction of multiple comparisons across the entire brain (e.g. a whole-brain gray matter mask [volume=1,459,304 mm^3]) as determined via simulation using the 3dClustSim utility (10,000 iterations); updated and 'bug-free' on December 2015; [https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html]; (Cox, 1996). Significance at corrected $\alpha < 0.05$ and a voxel threshold of $P < 0.001$ yielded a minimum cluster size of at least 120 contiguous voxels (volume=960 mm^3).

To test our hypotheses, we first conducted a whole-brain 2 (group) × 1 ANCOVA for Win > Loss, covarying for gender. We then conducted a planned ROI analysis in which BOLD signal activation during Win > Loss was extracted for each subject using left and right NAcc anatomical masks, defined via the AAL atlas and created using MARINA (http://www.bion.de/Marina.htm; (Walter *et al.*, 2003). The parameter estimates/β-weights were extracted for each participant from NAcc ROIs representing BOLD signal response (parameter estimates, arbitrary units [a.u.]) averaged across all voxels within the anatomical masks. Group differences were compared in SPSS using two ANOVAs (one for left NAcc and one for right NAcc) with group (BD and NBD), gender (male and female) and the interaction of group and gender as independent variables and the extracted BOLD signals (β-weights) as the dependent variables.

Next, to examine NAcc functional coupling during Win > Loss, we used a generalized form of context-dependent psychophysiological interaction analyses (gPPI; http://brainmap.wisc.edu/PPI, (McLaren *et al.*, 2012). The same anatomical left and right NAcc masks, described above, were used as the seeds-of-interest (SOIs). The deconvolved time series for each SOI were extracted for each subject to create the physiological variable. Condition onset times for Win, Loss and Fix events were separately convolved with the canonical hemodynamic response function for each condition, creating the psychological regressors. Finally, interaction terms (PPIs) were computed by multiplying the time series by the physiological variables. All physiological, psychological, and PPI terms were included as regressors in individual first-level models. Contrast images for Win > Loss were created for each subject and entered into second-level 2 (group) by 1 ANCOVAs, covarying for gender, for the left and right NAcc to determine whether there were group differences in NAcc FC. Given our *a priori* hypotheses, analyses were restricted to a predetermined anatomical mask consisting of the mPFC, OFC, anterior cingulate and dorsal cingulate; regions with known projections to the NAcc (Haber and Knutson, 2010; Britt *et al.*, 2012) and implicated in reward (Haber and Knutson, 2010) and addiction (Goldstein and Volkow, 2011). To correct for multiple comparisons, joint height and extent thresholds were determined via Monte Carlo simulations (10,000 iterations) using the 3dClustSim software described above and at corrected $\alpha < 0.05$ and a voxel threshold of $P < 0.001$ yielded a minimum cluster size of at least 21 contiguous voxels (volume=168 mm^3) for both the right and left NAcc FC. To detect the direction of group effects for the PPI analyses, we extracted parameter estimates/β-weights representing connectivity strength averaged across all voxels within a 10 mm radius sphere surrounding the peak activation/connectivity clusters of each participant.

RESULTS

Group differences

As shown in Table 1, BD were younger than NBD, but the groups did not differ on gender, ethnicity or race. Groups also did not differ on prevalence or cigarette use rate or marijuana use frequency in the past month. However, as expected, BD drank significantly more total drinks within the past month and reported more drinks per week than NBD, highlighting meaningful differences in drinking

Table 1. Participant characteristics

	Non-binge group, $n = 23$	Binge group, $n = 27$	*P*-value
Age	25.70 (2.95)	24.00 (2.24)	0.03
Gender (% Female)	43%	44%	0.59
Ethnicity (% Hispanic)	13%	15%	0.57
Race			0.16
% Caucasian	74%	47%	
% More than 1 Race	13%	19%	
% African-American	13%	19%	
% Asian	0%	15%	
Number of binges in past month	–	4.15 (2.63)	–
Average drinks per week	3.14 (2.28)	11.42 (6.51)	<0.001
Total drinks in past month	12.54 (9.12)	45.67 (26.02)	<0.001
% Smoked > 1 cigarette in past month	26%	33%	0.76
Average number of cigarettes per day	0.81 (1.57)	1.13 (2.15)	0.76
% Smoked Marijuana in past month	30%	48%	0.14
Frequency of Marijuana use*	6.50 (9.42)	4.27 (5.18)	0.46

Note: All values are means and standard deviations unless otherwise noted; $P < 0.05$. *Frequency defined as number of occasions within the past 30 days.

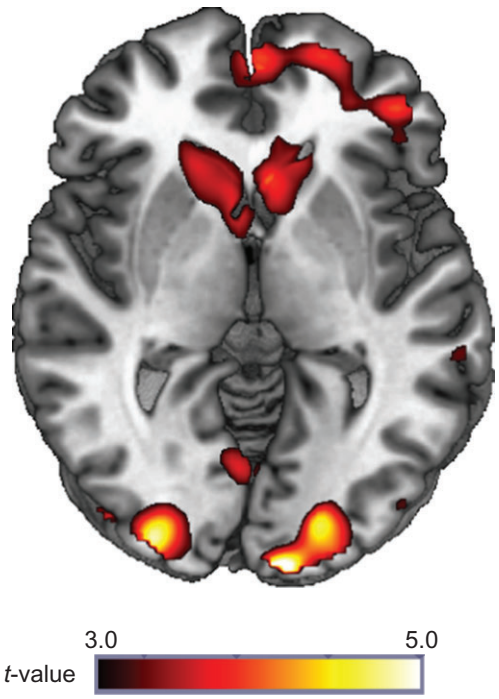

Fig. 1. Whole-brain task activation during reward. Whole-brain task activation ($P < 0.05$, corrected) for all subjects to reward (Win > Loss trials).

behaviors across the two groups. Of note, four NBD (17%) reported having a period in their life that they met criteria for binge drinking; however, on average this period was 5 years ago (range: 2–10 years ago) and they reported not bingeing since then. Therefore, although the groups were defined by binge drinking in the past month, NBD's current non-binge drinking pattern generally reflects their non-binge drinking pattern historically.

Task activation in NAcc and whole-brain group differences during reward

Results indicated that reward receipt relative to loss (Win > Loss) significantly activated a large contiguous cluster of frontal and mesolimbic reward regions, including bilateral NAcc, caudate and putamen (peak MNI [30, 30, 42], $k = 13{,}611$ voxels, $Z = 5.02$, $P < 0.05$, corrected). Mesolimbic activation during reward is illustrated in Fig. 1. All significant whole-brain peak clusters are shown in Table 2. Whole-brain search for group differences in activation during reward was not significant.

NAcc ROI analyses

BD exhibited greater activation in both the left and right NAcc during reward receipt relative to loss compared to NBD ($F(3,47) = 4.83$, $P = 0.03$; $F(3,47) = 6.07$, $P = 0.02$; respectively) (Fig. 2).

PPI analyses

The gPPI FC analyses revealed BD and NBD displayed divergent patterns of NAcc FC during reward relative to loss (Fig. 3). Specifically, BD exhibited reduced, negative bilateral NAcc–dACC FC compared with NBD, who showed positive NAcc–dACC FC during reward (left: MNI peak [−10, −2, 32], $k = 36$ voxels, $Z = 3.81$, $P < 0.05$, corrected and MNI peak [10, −16, 28], $k = 23$ voxels, $Z = 3.55$, $P < 0.05$ corrected; right: MNI peak [−10, −2, 32], $k = 40$ voxels, $Z = 3.85$, $P < 0.05$, corrected and MNI peak [12, −22, 30], $k = 51$ voxels, $Z = 3.71$, $P < 0.05$ corrected; Fig. 3). There were no other significant findings within the PFC mask. Scatterplots depicting how groups differ on NAcc–dACC FC and NAcc activation are shown in Supplemental Fig. 3.

Relationship between neural activation and drinking behavior

We ran correlations among extracted bilateral NAcc activation during reward relative to loss, extracted bilateral NAcc–dACC FC activation during reward relative to loss, and total number of drinks in the past month (square root transformed). Results indicated left and right NAcc activation during reward relative to loss was not significantly related to past month drinking ($r = 0.18$, $P = 0.21$; $r = 0.21$, $P = 0.14$, respectively). On the other hand, less right NAcc–dACC FC activation was associated with greater total drinks in the past month ($r = -0.29$, $P = 0.04$) and the relationship between less left NAcc–dACC FC activation and more total drinks in the past month trended toward significance ($r = -0.27$, $P = 0.06$) (Fig. 3).

Table 2. Whole-brain task activation for reward

Lobe	MNI coordinates			*Z* score	Voxels
	x	*y*	*z*		(*k*)
Frontal/subcortical					
Contiguous cluster extending from the bilateral middle frontal gyrus to the caudate	30	30	42	5.02	13,611
Parietal/temporal					
L Angular gyrus extending to the middle temporal gyrus	−40	−60	36	4.32	924
Occipital					
L Cuneus, middle occipital gyrus	−8	−102	4	5.09	513
R Middle and interior occipital gyrus, R Cuneus	30	−94	4	4.87	1089

Note: Reporting of all significant peak voxels at $P < 0.05$ whole-brain corrected with a cluster size of > 120 contiguous voxels. L = Left; R = Right; MNI = Montreal Neurologic Institute.

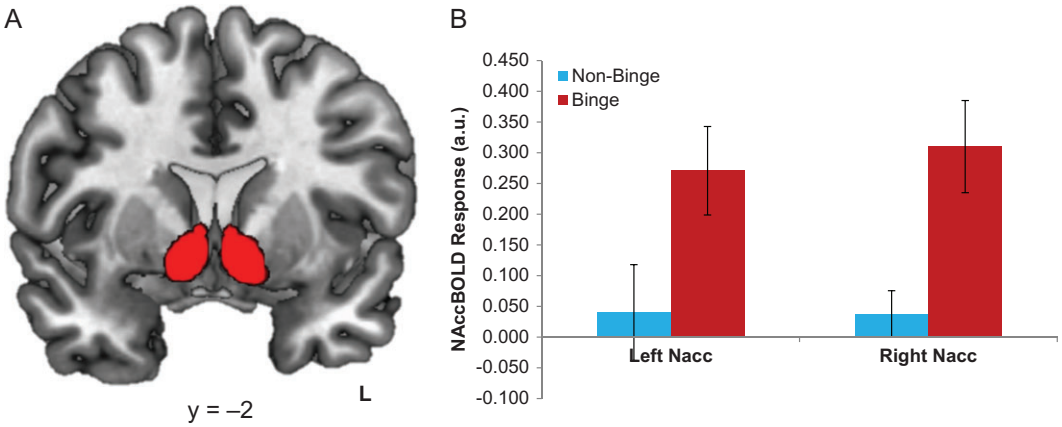

Fig. 2. Group differences in region-of-interest (ROI) NAcc BOLD reward reactivity. (A) Left and right NAcc ROI used (B) Extracted response (in β-weights/parameter estimates of activation) for each group from the left and right NAcc activation to reward (Win > Loss).

Post-hoc analyses controlling for age and post-hoc analyses examining NAcc activation, as well as NAcc FC activation during Win > Fix and Loss > Fix can be found in the supplement.

DISCUSSION

Altered brain reward circuitry has been implicated in individuals with AUD, but little is known about whether these alterations predate AUD, or whether they are present in at-risk current drinkers, such as BD. In this study, we examined reactivity to reward within the NAcc, a key node in the brain reward circuitry, and FC with the NAcc during reward in healthy at-risk BD compared to NBD. We found preliminary evidence that BD had more activation in the left and right NAcc during reward receipt relative to loss than NBD. Post-hoc analyses showed that this was driven by the difference between Win and Loss events, as neither condition alone significantly differed by group. In addition, BD displayed negative bilateral NAcc–dACC FC, while NBD displayed positive bilateral NAcc–dACC FC during reward receipt. Post-hoc analyses demonstrated that in addition to the difference between Win and Loss events in FC, BD had less FC between the right NAcc and right dACC and between the right NAcc and right superior frontral gyrus during Win > Fix compared to NBD. Furthermore, NAcc–dACC FC during Win > Loss was related to past month drinking, such that less right NAcc–dACC FC was associated with greater total drinks in the past month and this effect trended toward significance for left NAcc–dACC FC. This extends previous findings of greater activation in the striatum during alcohol cues and monetary reward receipt (Braus *et al.*, 2001; Myrick *et al.*, 2004; Wrase *et al.*, 2002, 2007) and greater negative FC between the NAcc and prefrontal regions during monetary reward receipt among individuals with AUD (Forbes *et al.*, 2014). It is also consistent with lower resting-state FC between the NAcc and the dACC in individuals with SUD (Hong *et al.*, 2009; Motzkin *et al.*, 2014). Thus, we show similar patterns of neural reactivity to reward in healthy, non-dependent young adult BD, who are at-risk for AUD, and found initial evidence that patterns of neural activation were related to past month drinking.

It is important to note that our primary findings were based on an ROI approach and were not based on whole-brain corrected analysis. In fact, we did not find whole-brain corrected group differences in NAcc activation to reward receipt. This is not unusual, several previous studies use ROI approaches (Forbes *et al.*, 2014), as current standards for whole-brain correction are conservative (Woo *et al.*, 2014; Eklund *et al.*, 2016) and often require large sample sizes to find effects. The present findings are therefore considered preliminary and require replication with larger samples.

Our results provide preliminary evidence that BD exhibit a stronger neural response to reward receipt relative to loss in the NAcc, a region implicated in the development and maintenance of AUD (Koob and Volkow, 2016). A larger difference in activation to rewards compared to losses may contribute to the continuation of risky drinking, eventually leading to AUD. Specifically, greater neural reactivity to rewards relative to losses may lead to increased hedonia and subjective pleasure from rewards (like alcohol), and/or insensitivity to losses

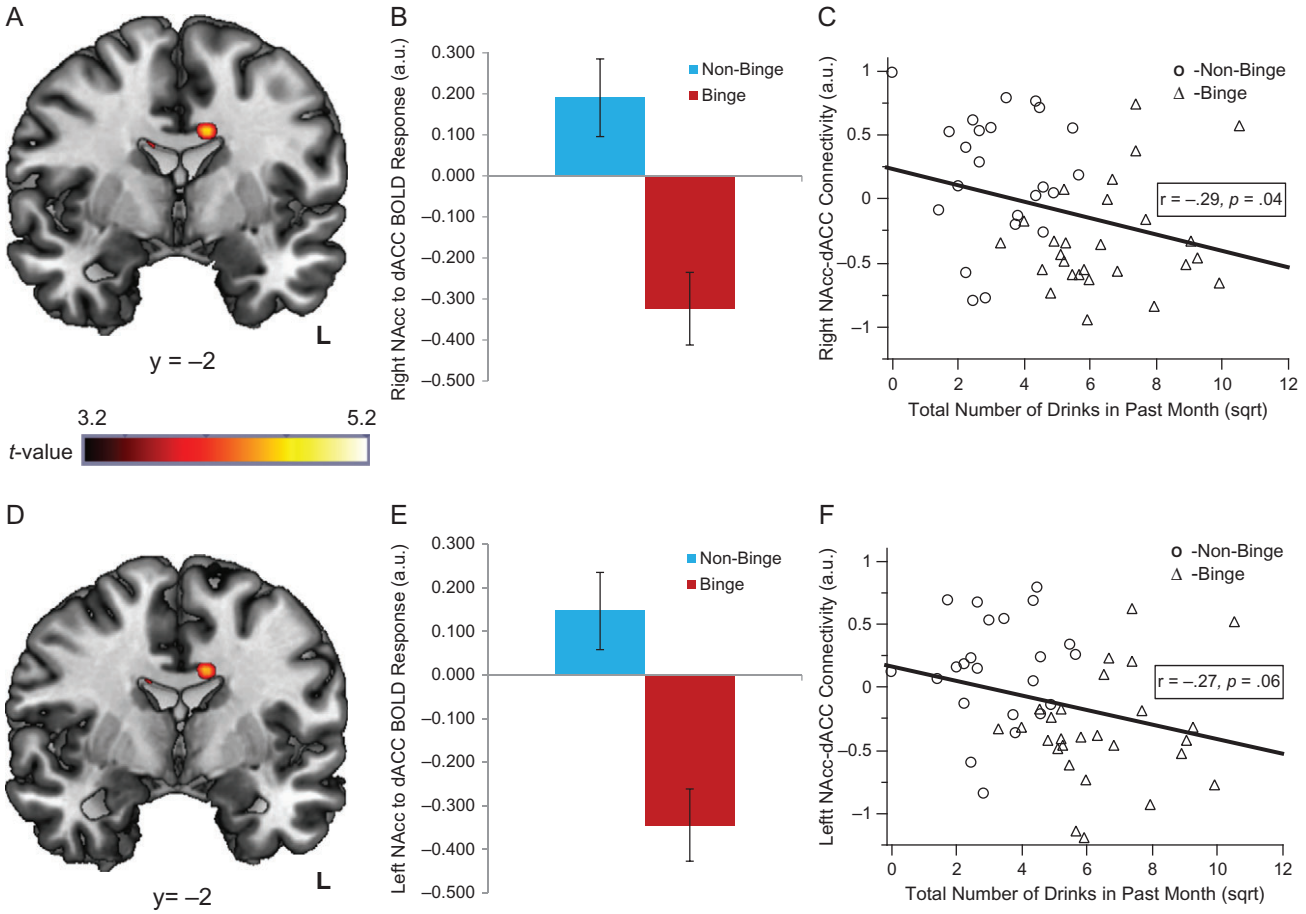

Fig. 3. Group differences in NAcc–dACC functional connectivity during reward. (A and D) Activation in the dACC, where Binge drinkers displayed negative right NAcc to bilateral dACC functional connectivity (A) and negative left NAcc to bilateral dACC functional connectivity (D), while non-binge drinkers showed positive connectivity between these regions ($P < 0.05$, corrected). (B) Group differences in extracted right NAcc to dACC BOLD functional connectivity. (E) Group differences in extracted left NAcc to dACC BOLD functional connectivity. (C and F) The relationship between past month drinking and right and left NAcc–dACC BOLD functional connectivity, respectively.

resulting in excessive reward seeking and increased risk-taking to pursue rewards including alcohol consumption. Of note, several factors may moderate this effect, including genes, gender, sex-steroids, family history and personality traits (Andrews *et al.*, 2011; Braams *et al.*, 2016; Nikolova *et al.*, 2013) and require further study.

We also observed inverse connectivity between the NAcc and the dACC, a region involved in cognitive control of behavior and emotion, in the two groups. BD showed negative NAcc–dACC FC, which may reflect deficient regulation of reward, as the NAcc and dACC circuit is implicated in affective regulation and the top-down inhibition of limbic regions (Haber and Knutson, 2010). Indeed, we found less NAcc–dACC connectivity is related to more drinks in the past month, suggesting NAcc–dACC connectivity plays an important role in modulating drinking behavior. Therefore, the dACC may have an impaired ability to modulate reward reactivity in the NAcc, leading to greater reward reactivity in the NAcc in BD. It is also possible that BD's greater reward reactivity in the NAcc may overwhelm the circuit and thus the modulation of the NAcc by the dACC is not strong enough to counteract the NAcc response.

Among individuals with AUD, less fronto-striatal FC during response inhibition is related to greater severity of AUD, indicating that strength of fronto-striatal circuitry is an important factor in the progression of AUD (Courtney *et al.*, 2013). Furthermore, previous evidence that reduced resting-state connectivity between the NAcc and dACC was associated with greater severity of nicotine dependence (Hong *et al.*, 2009; Motzkin *et al.*, 2014), indicates that NAcc–dACC connectivity may play an important role in addiction more generally and this may be especially true during reward and/or loss. It may be that decreased NAcc–dACC connectivity during reward receipt relative to loss reflects vulnerability for AUD, as BD may have difficulty appropriately engaging circuitry involved in reward and the regulation of behavior and emotion. It is also possible that dACC inhibitory inputs to the NAcc are a result of the neurotoxic effects of alcohol and this circuitry becomes more disrupted as alcohol use progresses.

To our knowledge, this is one of the first studies to examine disruptions in brain reward circuitry in non-dependent, healthy young adults at-risk for AUD. Our findings suggest disruptions in reward-related circuitry are present in healthy, high-risk individuals even before they develop AUD. However, the etiology of these disruptions is not known and it is possible the BD's prior heavy alcohol use has caused alterations in their brain function. Thus, the observed findings may due to the neuroadaptations or neurotoxic effects of alcohol rather than being pre-existing risk factors. Future prospective studies following individuals who are initially alcohol naive will be critical in delineating the extent to which aberrant neural reward reactivity is a risk factor, disease marker or scar.

The study also has limitations. First, the sample size was relatively small, limiting statistical power to find subtle effects. In addition, the study focused on participants' self-reported current drinking. Although lifetime SUD was exclusionary, other aspects of their prior substance use were not captured (e.g. age of first drink, extended periods of heavy drinking and lifetime drinks) and may have influenced the results. While the groups did not differ significantly in their use of other drugs (e.g. nicotine and marijuana), it is possible that BD differed on drug use measures not assessed here. Furthermore, we did not collect data on BOLD response to reward anticipation, making it difficult to compare our findings to other studies of AUD and risk for AUD (Heitzeg *et al.*, 2015). Moreover, we did not collect self-report measures of task engagement, which could affect the results. We also did not collect family history of AUD, which has been shown to influence NAcc activation to rewards, NAcc connectivity, and structural connectivity of reward regions (Heitzeg *et al.*, 2015). We would expect that BD are more likely to have a family history of AUD, but since this information was not captured, it is possible that the group differences we found may be more robust had we controlled for family history. Finally, gPPI analyses are correlational, so the directionality of NAcc–dACC connectivity cannot be determined.

CONCLUSIONS

Our study provides preliminary evidence that individuals at high risk for AUD display a neural pattern that mirrors individuals with active SUD such that they have greater NAcc reactivity, and reduced NAcc–dACC connectivity, to reward relative to loss. In addition, less NAcc–dACC connectivity was associated with more past month drinking. Therefore, individuals at high risk for AUD may have deficient regulation of their heightened responses to rewards relative to loss, which is related to their current drinking. When considered with previous studies, the current findings suggest that this profile of reward brain circuitry contributes to vulnerability for developing AUD and may therefore help to identify individual at-risk for AUD for intervention. The results also suggest that reactivity to natural reinforcers, as well as alcohol, may be an important therapeutic target within AUD prevention efforts.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Alcohol And Alcoholism* online.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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