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Association between impulsivity and neural activation to alcohol cues in heavy drinkers

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ABSTRACT

This study examines associations between two measures of impulsivity and brain response to alcohol taste cues. Impulsivity is both a risk factor for and a consequence of alcohol use and misuse. Frontostriatal circuits are linked to both impulsivity and addiction-related behaviors, including response to alcohol cues. Non-treatment-seeking heavy drinkers (n = 55) completed (i) an fMRI alcohol taste cue-reactivity paradigm; (ii) the monetary choice questionnaire (MCQ), a measure of choice impulsivity where participants choose between smaller, sooner rewards and larger, delayed rewards; (iii) and the UPPS-P Impulsive Behavior Scale, a self-report measure assessing five impulsivity factors. General linear models identified associations between neural alcohol taste cue-reactivity and impulsivity, adjusting for age, gender, and smoking status. Self-reported sensation seeking was positively associated with alcohol taste cue-elicited activation in frontostriatal regions, such that individuals who reported higher sensation seeking displayed greater neural response to alcohol taste cues. Conversely, delay discounting was negatively associated with activation in frontoparietal regions, such that individuals who reported greater discounting showed less cue-elicited activation. There were no significant associations between other self-reported impulsivity subscales and alcohol taste cue-reactivity. These results indicate that sensation seeking is associated with reward responsivity, while delay discounting is associated with recruitment of self-control circuitry.

1. Introduction

Impulsivity and cue reactivity are two central constructs to Substance Use Disorders (SUDs), including Alcohol Use Disorder (AUD). Although much of the extant literature on these constructs has examined them separately, findings indicate that they may share mechanisms via activity in the orbitofrontal cortex, prefrontal cortex, and nucleus accumbens (Jasinska et al., 2014). The limited body of research directly comparing impulsivity and cue reactivity suggests that they are indeed related, linking higher impulsivity to increased cue-elicited craving (Papachristou et al., 2014, 2013). What remain unknown are the shared and unique aspects of these constructs as well as their neural correlates. The current paper addresses this question in a sample of non-treatment seeking heavy drinkers.

Poor impulse control has been linked with all stages of substance use and misuse, including increased probability of initiation, rapid escalation, failing to cut down once use becomes problematic, and relapsing despite motivation to remain abstinent (Jentsch et al., 2014). Trait impulsivity is thought to act as both a risk factor for and a consequence of drug and alcohol consumption (Jentsch et al., 2014; Kozak et al., 2018). This bi-directional relationship between impulsivity and substance use acts through two inter-related phenomena. Firstly through enhanced cue reactivity, or the increased salience of the rewarding/reinforcing qualities of the desired substance stimulus, which occurs via increased subcortical dopamine transmission in mesolimbic areas; and secondly, a decreased ability to inhibit the impulse to seek out or use a substance at the cognitive level, or impaired frontocortical function (de Wit, 2009; Grant and Chamberlain, 2014; Jentsch and Taylor, 1999).

In AUD, trait impulsivity has been linked with alcohol consumption (Sanchez-Roige et al., 2019), cue-elicited craving for alcohol (Papachristou et al., 2013), and early onset of alcohol initiation

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(Jentsch et al., 2014). Previous neuroimaging studies have shown that alcohol addiction severity is positively correlated with alcohol cue-induced activity in mesocorticolimbic areas (Jasinska et al., 2014) and negatively correlated with activity in cognitive control regions during an impulsivity-measuring task (Lim et al., 2017). In sum, impulsivity and drug and alcohol use are closely related, so much so that impulsivity has been proposed as an endophenotype for these disorders (MacKillop, 2013; Sanchez-Roige et al., 2019).

In humans, assessment of impulsivity involves self-report scales as well as behavioral tasks – with these two approaches not being strongly associated with each other (Jentsch et al., 2014). One such self-report measure, the UPPS-P Impulsive Behavior Scale, breaks impulsivity down into five subscales: negative urgency (tendency to act rashly under extreme negative emotions), lack of premeditation (tendency to act without thinking), lack of perseverance (inability to remain focused on a task), sensation seeking (tendency to seek out novel and thrilling experiences), and positive urgency (tendency to act rashly under extreme positive emotions) (Cyders et al., 2007). There is strong evidence for an underlying neurobiology subserving UPPS-P impulsivity traits. Multiple subscales from the UPPS-P showed strong genetic correlations with drug experimentation and other substance use traits including smoking initiation and lifetime cannabis use. Specifically, a positive genetic correlation through the CADM2 gene was observed between sensation seeking, positive urgency, and lack of premeditation and alcohol consumption (Sanchez-Roige et al., 2019). Sensation seeking is also specifically associated with activation of brain regions related to motivation, arousal, and reinforcement, such as the orbitofrontal cortex and insula (Kozak et al., 2018). Another study found that negative urgency correlates with increased alcohol abuse beyond other facets of impulsivity (Chester et al., 2016).

As for more behavioral measures of impulsivity, delayed reward discounting (DRD) has received substantial support, particularly with regards to its association with addictive behaviors and disorders (Athamneh et al., 2019; de Wit, 2009; Loree et al., 2015; Reynolds, 2006). DRD is an index of impulsive decision-making based in behavioral economics that reflects how rapidly a reward loses its value based on a delay in time; specifically, individuals are asked to make a series of decisions between smaller-sooner rewards and larger-later rewards (Lim et al., 2017). SUD manifests as persistent preferences for the immediate rewarding effects of the drug at the cost of substantial future benefits from not using (MacKillop et al., 2011). DRD has been shown to be significantly greater in substance use case groups compared to controls (MacKillop et al., 2011). Increased propensity for delay discounting is also correlated both with family history and with early onset of alcohol and smoking initiation, and, in animal models, exposure to stimulant drugs increases delay discounting (Jentsch et al., 2014). Additionally, more impulsive delay discounting in a DRD task including both monetary and cigarette rewards predicts the onset of smoking over the course of adolescence, as well as smoking cessation outcomes (MacKillop et al., 2012). Homologous brain regions in human and animal studies have been shown to subserve delay-related decision making, including the orbitofrontal cortex, prefrontal cortex, nucleus accumbens, medial temporal gyrus, hippocampus/entorhinal cortex, and amygdala (Jentsch et al., 2014; Owens et al., 2017)

Another important way in which impulsivity may be related to AUD phenotypes is the intersection between impulsivity and alcohol cue reactivity. Higher impulsivity has been linked to stronger cue-elicited craving for alcohol, predicting both tonic and phasic craving in response to cue exposure (Papachristou et al., 2014, 2013). Compared to non-dependent drinkers, dependent drinkers scored higher on trait measures of impulsivity and showed increases in self-reported craving, skin conductance, and heart rate when exposed to alcohol cues, supporting the claim that interactions between impulsivity and cue reactivity may characterize alcohol use motivation in dependent drinkers (Subotic et al., 2014). Another recent study (Sommer et al., 2017) showed that individuals with higher impulsivity as measured using DRD had stronger Pavlovian reactivity to visual alcohol cues.

Neural substrates of cue reactivity, in turn, are thought to predict relapse in individuals with AUD (Loree et al., 2015). Alcohol cues activate limbic and prefrontal regions, including the ventral striatum / nucleus accumbens, medial frontal gyrus, orbitofrontal cortex, prefrontal cortex, and anterior cingulate cortex among individuals with AUD. Further, individuals with AUD also show increased activation in response to alcohol cues in temporoparietal areas such as the posterior cingulate cortex, precuneus, cuneus, and superior temporal gyrus, compared to healthy controls (Schacht et al., 2013). Previous fMRI studies point to the interplay between mesolimbic, frontocortical, and nigrostriatal circuits as underlying cue reactivity. Cue-induced activation within these circuits is correlated with alcohol addiction severity, years of drinking, intensity of alcohol use, and self-reported craving (Jasinska et al., 2014).

Mesolimbic areas play a key role in drug seeking behavior due to primary drug reinforcement, which acts as an unconditioned reward-related stimulus. Increased dopamine release within the nucleus accumbens is produced by repeated substance use, while acquisition of related stimulus-reward associations that contribute to conditioned reinforcement are enhanced by adaptations in the amygdala. These subcortical changes contribute to an enhanced drug-seeking impulse (Everitt, 2014; Jentsch and Taylor, 1999). Additionally, the initiation of substance use usually occurs during adolescence, which is a high-risk period for the development of SUD due to the immaturity of prefrontal cortical systems responsible for impulse control (Kozak et al., 2018). Neuroadaptations to frontal cortical regions that are activated by cue-induced cravings, including the orbitofrontal cortex and medial prefrontal cortex, leads to impairment in inhibitory control, such as a tendency to preferentially prefer smaller, immediate rewards over larger, delayed rewards in DRD tasks (Białaszek et al., 2017; Damasio et al., 1996). Connectivity between the lateral prefrontal cortex and striatum has also been shown to be associated with lower temporal discounting (van den Bos et al., 2014). Dopamine release in the prefrontal cortex may temporarily block its “inhibitory control” influence, allowing rapid learning and response by subcortical areas to palatable stimuli (Jentsch and Taylor, 1999).

The present study examines the intersection between impulsivity and neural substrates of alcohol cue reactivity in a sample of non-treatment seeking heavy drinkers. Specifically, this study tests the association between measures of impulsivity – both choice, via delayed reward discounting task, and self-reported, via UPSS-P – and alcohol cue reactivity during an fMRI alcohol taste cues task. We hypothesized that more impulsive individuals would display stronger BOLD activation of reward circuitry during alcohol taste cue presentation, as compared to less impulsive individuals.

2. Methods

2.1. Participants and screening procedures

Participants were recruited between November 2015 and February 2017 from the greater Los Angeles metropolitan area via study advertisements. Detailed methodology of the general screening and experimental procedures has been published elsewhere (Grodin et al., 2019). Briefly, participants were non-treatment-seeking heavy drinkers with inclusion criteria as follows: (i) engaged in regular heavy drinking, as indicated by consuming 5 or more drinks per occasion for men or 4 or more drinks per occasion for women at least 4 times in the month prior to enrollment (as indicated on the Timeline Follow-back (TLFB; Sobell and Sobell, 1992); or (ii) a score of ≥ 8 on the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993).

Eligibility was initially assessed through a telephone interview, after which eligible participants underwent additional screening in the laboratory. Participants read and signed an informed consent form upon arrival, then completed a number of individual differences measures

and interviews, including a demographics questionnaire, the AUDIT, Penn Alcohol Cravings Scale (PACS; Flannery et al., 1999), Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991) and the TLFB to assess for quantity and frequency of drinking over the past 30 days. AUD severity was determined as according to DSM-V diagnosis criteria after a clinical diagnostic interview completed by master's level clinicians. All participants were required to test negative on a urine drug test (except for cannabis).

A total of 120 participants were screened in the laboratory for eligibility, 38 did not meet inclusion criteria and 12 elected not to participate, leaving 60 participants who were enrolled and randomized. Of these, 55 participants underwent neuroimaging and are included in the present analyses.

2.2. Study design

Participants were assessed at 3 time-points: at baseline, at randomization, and 1-month follow-up. During the randomization visit, participants were randomly assigned to receive a 1-session brief drinking intervention or to an attention-matched control condition. Immediately following the intervention or control session, participants completed a functional magnetic resonance imaging (fMRI) scan to assess brain activity during exposure to alcohol and water taste cues. There were no significant group differences between the brief drinking intervention and attention-matched control groups (Grodin et al., 2019), therefore the groups have been combined for the present study. Participants returned for a follow-up visit approximately 4 weeks after the intervention or control session to assess alcohol use. Participants who completed all study visits were compensated $160.

2.3. Questionnaires

Impulsivity measures were collected during the baseline study visit. Trait impulsivity was measured by the UPPS-P Impulsive Behavior Scale (Cyders et al., 2007) and the Monetary Choice Questionnaire (MCQ – a delayed reward discounting task; (Kaplan et al., 2014), a series of choice questions scored to yield a measure of decision impulsivity. Of note, reward amounts were hypothetical and not tied to participant compensation. Separate scores were calculated for each subscale of the UPPS-P. The DRD function has unique scoring system as it is not consistent over time, but rather a hyperbola-like function so that the reward disproportionately gains value as the time to receipt approaches and disproportionately loses value when initially delayed. The hyperbolic function is characterized by the equation $V_d = V/(1 + kd)$ in which V_d is the present discounted value of the reward, V is the objective value of the reward, k is a constant that reflects the rate of discounting and d is the temporal delay. Therefore, a higher k value indicates a more impulsive tendency to prefer smaller, immediate rewards over larger, future rewards. As k is not normally distributed, we used ln(k) as the interpretable MCQ score (Lim et al., 2017; Simpson and Vuchinich, 2000).

2.4. Neuroimaging procedures

In order to undergo the fMRI scan, participants were required to have a BrAC of 0.00 g/dL and a urine toxicology screen negative for all drugs (excluding marijuana). Female participants were also required to have a negative pregnancy test.

Neuroimaging data were acquired on a 3.0T Siemens Prisma scanner at the UCLA Staglin Center for Cognitive Neuroscience. Detailed methodology of the neuroimaging protocol have been published elsewhere (Grodin et al., 2019). Briefly, the neuroimaging protocol consisted of a high-resolution, matched-bandwidth (MBW) scan and a structural magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scan. These were followed by two runs of a modified version of the Alcohol Cues Task, which involves the oral delivery of alcohol or control (water) tastes to elicit physiological reward responses (Filbey et al., 2008). The alcohol cues task was administered over the course of 2 runs with 50 trials/run.

Preprocessing of the neuroimaging data followed conventional procedures implemented in FMRIB's Software Library (FSL 5.0) (www.fmrib.ox.ac.uk/fsl). This included motion correction [Motion Correction Linear Image Registration Tool (McFLIRT, Version 5.0)], high-pass temporal filtering (100 s cutoff) using FSL's FMRI Expert Analysis Tool (FEAT, Version 6.00), and smoothing with a 5 mm full width half maximum Gaussian kernel. FSL's Brain Extract Tool (BET) was used to remove skull and non-brain tissue from both the structural and functional scans. Data were denoised using ICA-AROMA (Pruim et al., 2015) using a non-aggressive approach to reduce motion artifacts associated with swallowing.

2.5. Data analysis

SPSS 24 was used to investigate correlations between measures of impulsivity (i.e. DRD and UPPS-P subscales). The analysis of the Alcohol Cues Task was conducted using FSL's FEAT as described in (Grodin et al., 2019). In brief, alcohol and water taste cues were convolved with a double-gamma hemodynamic response function (HRF). Six motion regressors were included as regressors of noninterest. Data for each subject were registered to the MBW, followed by the MPRAGE using affine linear transformations, and then were normalized to the Montreal Neurological Institute (MNI avg152) template. Registration was refined using FSL's non-linear registration tool. The primary contrast of interest, the Alcohol Taste Cue > Control Taste Cue contrast, was defined in the first-level models. The second-level model combined the contrast images across the two task runs and the third-level model combined the contrast images between subjects. To evaluate if trait impulsivity was associated with brain activation to alcohol taste cues, GLMs correlating DRD or UPPS-P subscales with the alcohol taste > water taste contrast were run across all subjects. Age, sex, and cigarette smoking status were entered as covariates. Z-statistic images were thresholded using a cluster threshold of $Z > 2.3$ and a (corrected) cluster significance threshold of $P < 0.05$ (Worsley, 2001).

3. Results

3.1. Demographics

Participants included 55 non-treatment-seeking heavy drinkers, with a mean age of 34.22. Twenty-three were female, 27 were cigarette smokers as defined by the FTND, and the sample had, on average, moderate-to-severe alcohol use disorder. Specifically, the majority of our sample met diagnostic criteria for a current (past 3-month) AUD upon completion of the structured diagnostic interview. Participants' average ln(k) of −4.19 was equivalent to setting the present discounted value of $90.41 as equal to the future value of $100 in 7 days (see

Table 1
Participant Characteristics (n = 55).

Variable	Mean (SD)
Age	34.22 (12.11)
Sex (m/f)	32/23
Cigarette Smokers (n)	27
Monetary Choice Questionnaire ln(k)	−4.19 (1.63)
UPPS-P Negative Urgency Score	8.51 (2.67)
UPPS-P Lack of Perseverance Score	7.45 (2.25)
UPPS-P Lack of Premeditation Score	7.24 (2.21)
UPPS-P Sensation Seeking Score	11.45 (2.83)
UPPS-P Positive Urgency Score	7.24 (2.52)
AUDIT Total Score	17.41 (7.13)
PACS Total Score	19.27 (6.96)
AUD Severity (No Diagnosis/Mild/Moderate/Severe)	6/19/14/16

Table 2
Intercorrelations between UPPS-P Subscales and MCQ ln(k).

	1	2	3	4	5
1. MCQ ln(k)	–				
2. UPPS-P Negative Urgency	.16				
3. UPPS-P Lack of Perseverance	.03	.36*			
4. UPPS-P Lack of Premeditation	.21	.36*	.60*		
5. UPPS-P Sensation Seeking	−0.02	−0.07	−0.14	−0.02	
6. UPPS-P Positive Urgency	−0.01	.49*	.07	.24	.37*

Note. MCQ = Monetary Choice Questionnaire.
* $p < 0.01$ (No comparisons $0.01 < p < 0.05$).

Table 1 for complete list of participant characteristics, including impulsivity scores).

Participants' scores on self-reported measures of trait and choice impulsivity (i.e. UPPS-P and MCQ) were not significantly correlated, though certain sub-scales within the UPPS-P were correlated with each other (see Table 2).

3.2. Association between self-report impulsivity and alcohol taste cue reactivity

The UPPS-P sensation seeking subscale was positively associated with brain activation to alcohol taste cues in striatal and limbic regions including the pallidum, thalamus, insula, caudate, and paracingulate gyrus (see Fig. 1 and Table 3 for complete list of regions and cluster activation; Z-statistics are whole-brain cluster corrected, $Z > 2.3$, $p < 0.05$). There were no significant negative associations between sensation seeking scores and alcohol cue reactivity. Additionally, there were no significant associations, positive or negative, between other UPPS-P subscales and alcohol taste cue reactivity.

3.3. Association between choice impulsivity and alcohol taste cue reactivity

DRD, as measured by the Monetary Choice Questionnaire ln(k), was negatively associated with alcohol taste cue reactivity in frontoparietal regions including the precuneus, posterior cingulate, middle frontal gyrus, and occipital cortex (see Fig. 2 and Table 4 for complete list of regions and cluster activation, Z-statistics are whole-brain cluster corrected, $Z > 2.3$, $p < 0.05$). There were no significant positive associations between DRD scores and alcohol taste cue reactivity.

4. Discussion

This study examined the relationship between impulsivity and alcohol taste cue reactivity in non-treatment-seeking heavy drinkers. Specifically, this study evaluated relationships between a self-report measure of trait impulsivity, through the UPPS-P, and impulsive decision-making, through DRD, and alcohol taste cue reactivity. Measures of choice impulsivity and self-report impulsivity were not significantly intercorrelated. We found that the sensation seeking subscale of the UPPS-P was positively associated with alcohol taste cue elicited brain activation in frontostriatal circuitry. We also found that DRD scores were negatively associated with alcohol taste cue elicited brain activation in frontoparietal circuitry.

As hypothesized, scores on the sensation seeking subscale of the UPPS-P were positively associated with neural activation in frontostriatal brain regions in response to alcohol taste cues. Conversely, negative urgency, lack of premeditation, lack of perseverance, and positive urgency subscales did not show significant associations with neural alcohol taste cue reactivity. Sensation seeking reflects a tendency to seek out novel sensations and experiences (Hittner and Swickert, 2006). In animal models, operant sensation seeking increases dopamine release in the striatum (Olsen and Winder, 2009; Rebec et al., 1997). In the present study, sensation seeking was positively associated with frontostriatal activation in response to alcohol taste cues, such that individuals with higher sensation seeking had greater neural reactivity in dopaminergic frontostriatal circuity, potentially reflective of an alcohol craving response. This is consistent with findings from the preclinical and clinical literature on sensation seeking. In animals, novelty-seeking behaviors were enhanced in alcohol-preferring compared to non-alcohol preferring rats (Nowak et al., 2000). In young adults, individuals with high scores on the sensation seeking subscale also have high alcohol use (Magid and Colder, 2007). Moreover, both baseline sensation seeking scores and slower reductions in sensation seeking over time prospectively predict the later development of an AUD in high-risk young adults (Quinn and Harden, 2013; Sher et al., 2000), and sensation seeking has been shown in a meta-analysis to be moderately correlated with alcohol use (Hittner and Swickert, 2006). Our finding contrasts with an earlier study which found a positive association between negative urgency and caudate activation to alcohol cues (Chester et al., 2016). However, methodological differences, including cue presentation and subject characteristics (non-AUD vs. AUD), may account for the discrepancy in findings and should be considered further.

In contrast to our hypotheses, delay discounting scores were negatively associated with alcohol taste cue elicited brain activation in frontoparietal regions, such that individuals who discounted rewards at a greater rate had less neural response to alcohol cues in the precuneus, posterior cingulate, and middle frontal gyrus. In fMRI DRD tasks, the posterior cingulate and cuneus are more activated when individuals select delayed rewards compared to smaller sooner rewards (Wittmann et al., 2007), which is similar to the pattern seen in the current study, albeit without the presence of alcohol cues. Further, in individuals with an AUD, decisions for delayed rewards activate cognitive control circuitry, and individuals with more severe alcohol use problems demonstrate greater neural response in the precuneus, among other brain regions (Claus et al., 2011). Together, this suggests that the negative association identified in the present study may represent the activation of cognitive control circuitry in response to alcohol taste cues, such that individuals who are less impulsive on the DRD questionnaire also activate top-down control circuitry when presented with alcohol taste cues. Alternatively, the negative association between delay discounting scores and frontoparietal activation to alcohol taste cues may reflect the recruitment of the default mode network (DMN). The DMN is a large-scale brain network implicated in self-reflective and prospective thought whose hubs include the precuneus, posterior cingulate, and medial prefrontal cortex (Raichle et al., 2001). The DMN is more activated when individuals think about the future (Buckner et al., 2008), and episodic future imagination reduces delay discounting via activation of a network akin to DMN (Hu et al., 2017), though some studies have found that discount rates are positively associated with Hurst exponent of DMN and Salience Networks (Chen et al., 2017) and connectivity of DMN and Cingulo-Opercular Networks (Chen et al., 2018). Within this mixed literature context, individuals in the present study who valued larger, later rewards demonstrated greater activation of a similar circuit during alcohol cue reactivity, potentially reflecting future thinking during alcohol taste cue reactivity.

The opposing direction of the associations between impulsivity measures and neural alcohol taste cue reactivity is supported by the lack of association between sensation seeking scores and delay discounting scores in this sample. This indicates that these scales are measuring discrete aspects of impulsivity. Previous studies have explored the multidimensional nature of impulsivity, suggesting that measures of impulsivity can be divided into three distinct categories: impulsive choice, impulsive action, and impulsive personality traits (MacKillop et al., 2016). The UPPS-P and MCQ measures used in this study fall into different assessment categories. While UPPS-P measures impulsive personality traits, delay discounting tasks focus on impulsive choice, using fungible rewards (i.e. money) as a proxy for rewarding substances – in this case, alcohol – to which subjects have been shown

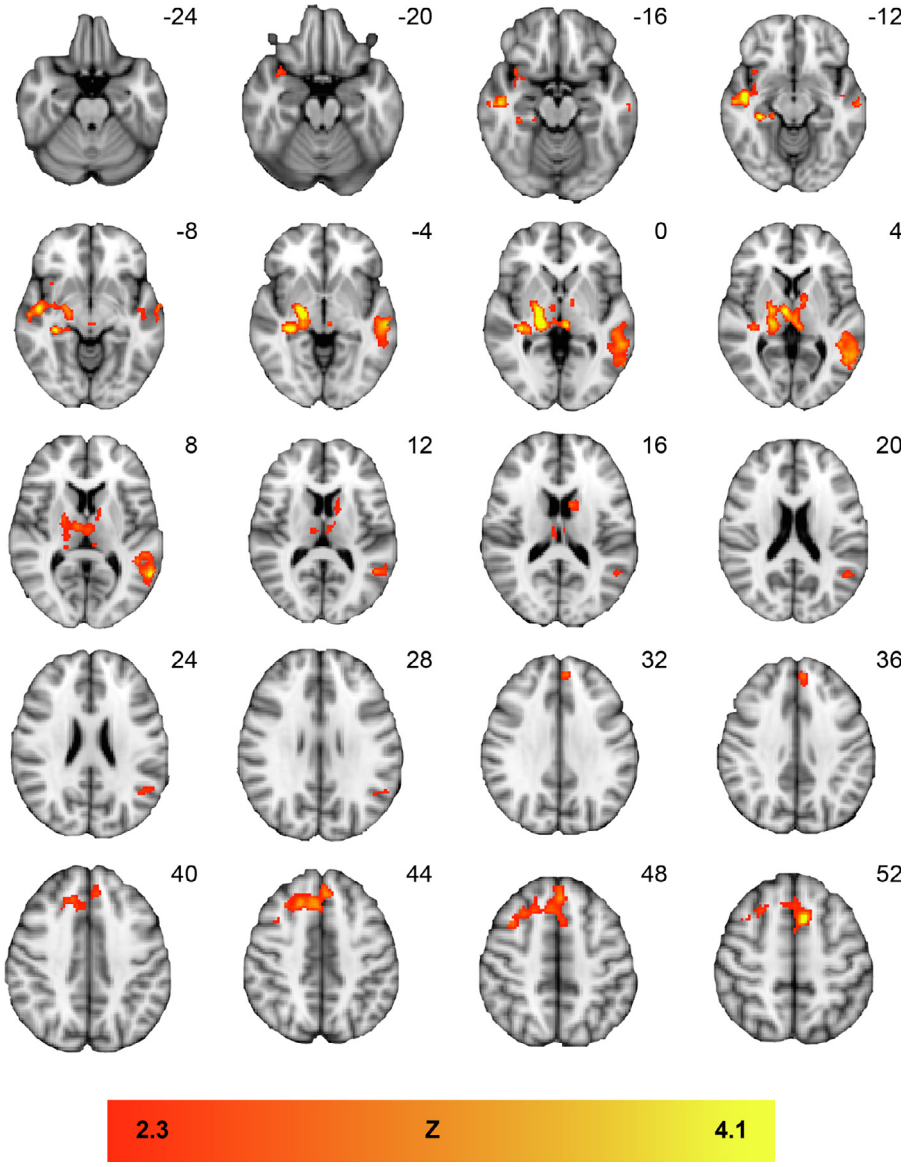

Fig. 1. UPPS-P Sensation Seeking and Cue-Reactivity.
The association between UPPS-P sensation seeking subscale and brain activation to alcohol taste cues. Sensation seeking was positively associated with activation in the pallidum, thalamus, insula, and paracincgulate gyrus. See Table 3 for a full list of significant regions. *Z*-statistic maps are whole-brain cluster corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space. Brain is displayed in radiological convention ($L = R$). .

Table 3
Association between UPPS-P Sensation Seeking Subscale and Brain Activation to Alcohol vs. Water Taste Cues.

Brain region	Cluster voxels	Max. *Z*	*x*	*y*	*z*
Positive association					
R Pallidum	1886	4.16	20	−14	−2
R Thalamus		3.55	6	−12	6
R Insula		3.25	38	−22	2
L Thalamus		2.69	−10	−30	6
L Caudate		2.66	−10	6	14
L Superior Frontal Gyrus	1248	3.92	−6	12	54
L Paracingulate Gyrus		3.29	−4	8	54
L Middle Temporal Gyrus	1215	3.67	−58	−54	8
L Lateral Occipital Cortex		3.19	−58	−58	8

to respond accordingly (Amlung and MacKillop, 2011). Finally, while there exists some inconsistency in results of DRD studies, meta-analyses have consistently demonstrated across substances that delay discounting is a risk factor for addiction. (Amlung et al., 2017; Bickel et al., 2019).

The present results should be considered in light of its strengths and limitations. The study includes a sizable sample of heavy drinkers, as well as multiple measurements of impulsivity. Notably the fMRI task used in this study was a modified version of the original Alcohol Cues Task and did not elicit a strong reward activation signal in the brain. Future studies should utilize more widely-used alcohol cue paradigms, such as visual alcohol cue reactivity tasks (Grodin and Ray, 2019; Schacht et al., 2013), to replicate the impulsivity associations found herein and examine whether these results hold across the spectrum of alcohol cue reactivity tasks. Moreover, impulsivity has been identified as a risk-factor for AUDs as well as a consequence of alcohol misuse. As this study was cross-sectional in nature, it cannot disentangle the complex causal relationship between impulsivity and AUD.

In conclusion, this study sought to explore the interactions between impulsivity and neural alcohol taste cue reactivity in a sample of non-treatment-seeking heavy drinkers. The present study found distinct associations between sensation seeking and alcohol cue elicited neural

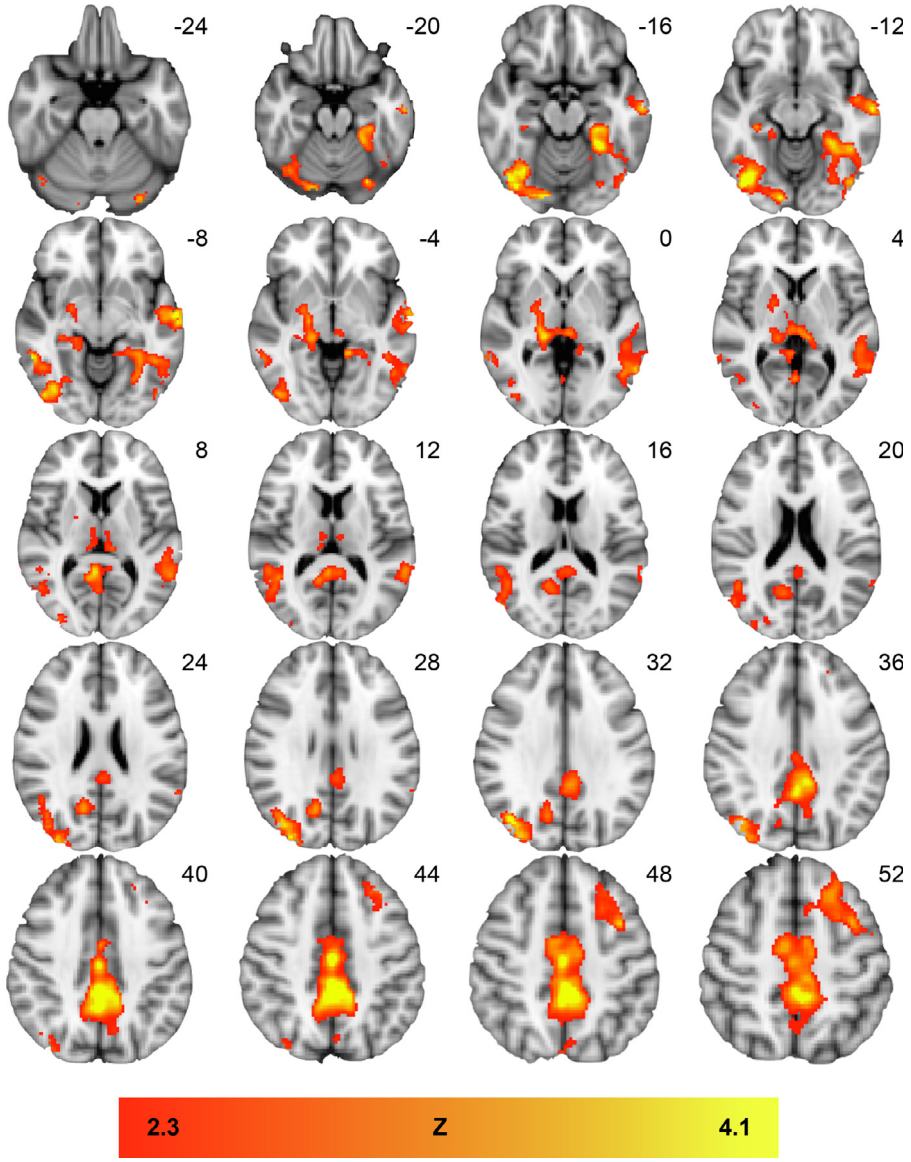

Fig. 2. Delayed Reward Discounting and Cue Reactivity.
The association between delay discounting (MCQ ln(k)) and brain activation to alcohol taste cues. Delay discounting was negatively associated with activation in the precuneus, posterior cingulate, middle frontal gyrus, and occipital cortex. See Table 4 for a full list of significant regions. *Z*-statistic maps are whole-brain cluster corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space. Brain is displayed in radiological convention ($L = R$).

Table 4
Association Between Monetary Choice Questionnaire ln(*k*) and Brain Activation to Alcohol vs. Water Taste Cues.

Brain region	Cluster voxels	Max. *Z*	*x*	*y*	*z*
Negative association					
L Precuneus	8120	4.51	−4	−40	48
R Posterior Cingulate Gyrus		4.11	2	−38	44
L Posterior Cingulate Gyrus		4.03	0	−18	44
R Precuneus		3.76	4	−46	44
R Lateral Occipital Cortex	2567	4.11	42	−74	−12
R Fusiform Gyrus		3.95	38	−72	−12
L Middle Frontal Gyrus	1098	3.93	−34	2	64

response and delay discounting and alcohol cue elicited neural response. Sensation seeking was positively associated with activation in frontostriatal circuitry, indicating an association between increases in novelty seeking with increases in reward responsivity; whereas delay discounting was negatively associated with activation in frontoparietal circuitry, potentially indicating an association between less impulsive decision making and increases in cognitive control.

CRediT authorship contribution statement

Elizabeth M. Burnette: Writing - original draft. **Erica N. Grodin:** Writing - original draft. **Aaron C. Lim:** Methodology, Writing - original draft. **James MacKillop:** Conceptualization. **Mitchell P. Karno:** Conceptualization. **Lara A. Ray:** Conceptualization, Methodology, Writing - original draft.

Declaration of Competing Interest

None of the authors have any conflicts of interest or financial disclosures.

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