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Article

Pain Catastrophizing Is Associated With Increased Alcohol Cue-Elicited Neural Activity Among Individuals With Alcohol Use Disorder

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Abstract

Aims: The current study examined the association between pain catastrophizing and alcohol cue-elicited brain activation in individuals with alcohol use disorder (AUD).

Methods: Non-treatment seeking heavy drinkers with AUD ($n = 45$; 28 males) completed self-report measures of pain catastrophizing and alcohol use/problems as part of a clinical trial of the neuroimmune modulator ibudilast. Participants were randomized to either placebo ($n = 25$) or ibudilast ($n = 20$) and completed an functional magnetic resonance imaging (fMRI) scan to assess neural activation to alcohol cues 1 week into the medication trial. Multiple linear regression examined whether pain catastrophizing predicted cue-induced activation in *a priori* regions of interest, namely the dorsal and ventral striatum (VS). An exploratory whole-brain analysis was conducted to assess the relationship between pain catastrophizing and neural alcohol cue reactivity.

Results: Pain catastrophizing predicted greater cue-induced activation in the dorsal ($b = 0.006$; $P = 0.03$) but not VS controlling for medication. Pain catastrophizing was positively associated with neural activation to alcohol cues in regions including the bilateral thalamus, left precuneus and left frontal pole.

Conclusion: Greater pain catastrophizing is associated with greater cue-induced neural activation in brain regions sub-serving habits and compulsive alcohol use. These findings provide initial support for a neural mechanism by which pain catastrophizing may drive alcohol craving among individuals with AUD.

Keywords: alcohol use disorder, heavy drinking, cue-reactivity, alcohol craving, pain

INTRODUCTION

Alcohol use disorder (AUD) and pain are comorbid, prevalent and costly conditions (Edwards *et al.*, 2020). It is estimated that 30–50% of individuals who seek treatment for AUD report recurring pain (Jakubczyk *et al.*, 2015; Boissoneault *et al.*, 2019). Individuals with chronic pain report greater alcohol use and greater incidences of AUD than the general population (Vowles *et al.*, 2018). Most of this literature is focused on subjective (self-reported) pain experiences; however, understanding the psychological factors that connect pain to AUD may reveal important constructs that further explain this complex relationship.

Pain catastrophizing is a psychological factor that influences the way in which individuals perceive and react to their pain (Sullivan *et al.*, 2001; Keefe *et al.*, 2004). Pain catastrophizing refers to a maladaptive cognitive response that is characterized by an anxious interpretation of pain that encompasses both perceived threat from pain and the perceived ability to tolerate or cope with pain (Sullivan *et al.*, 1995). While pain catastrophizing is related to other negative emotionality constructs (Leung, 2012); it remains its own unique trait-like entity independent of depression and anxiety (Geisser *et al.*, 1994; Sullivan *et al.*, 1998; Keefe *et al.*, 2000). While studies examining the relationship between pain catastrophizing and alcohol-related behaviors are in their infancy, higher levels of pain catastrophizing have been associated with AUD (Ciccone *et al.*, 2010).

Pain catastrophizing might contribute to greater alcohol use because individuals use alcohol to cope with physical pain, which is magnified by increased pain catastrophizing and negative affect. Related to this, our laboratory recently found that pain catastrophizing is associated with greater depressive symptomatology, alcohol-related problems and self-reported drinking to feel normal among individuals who report heavy alcohol drinking and low to moderate chronic pain (Nieto *et al.*, 2020). Additionally, pain catastrophizing predicted tonic (unprovoked) alcohol craving after controlling for demographic variables, depressive symptomatology and pain intensity (Nieto *et al.*, 2020). A logical next step would be to examine whether pain catastrophizing influences provoked alcohol cue-reactivity. A phasic (provoked) cue-reactivity protocol combined with neuroimaging would elucidate underlying neural circuits linking pain catastrophizing to the incentive salience of alcohol cues.

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Overlapping neural substrates and neurotransmitter systems play a dual role in AUD and pain transmission (Egli *et al.*, 2012). For example, the ventral striatum (VS) mediates the initial reinforcing actions of alcohol (Di Chiara and Imperato, 1988; Boileau *et al.*, 2003) and is activated by noxious stimuli (Baliki *et al.*, 2010; Gear and Levine, 2011). The dorsal striatum (DS) is proposed to underlie compulsive and habitual addiction behaviors in individuals with AUD (Everitt and Robbins, 2005; Pennartz *et al.*, 2011), as well as mediating analgesia (Magnusson and Fisher, 2000; Barceló *et al.*, 2012). However, studies examining the relationship between pain constructs and alcohol cue-elicited neural activation among individuals with AUD are critically lacking. Whether there is an association between pain catastrophizing and neural responses to alcohol cues among individuals with AUD is a promising area for future research.

The purpose of the current study was to examine the role of pain catastrophizing among individuals with AUD who completed a functional neuroimaging alcohol cue-reactivity task. Based on previous work from our laboratory indicating that pain catastrophizing is associated with heavy drinking to feel normal rather than for the reinforcing effects of alcohol (Nieto *et al.*, 2020), we hypothesized that pain catastrophizing would predict greater alcohol cue-induced activity in the DS, but not the VS. As an exploratory aim we conducted a whole-brain analysis to identify associations between pain catastrophizing and alcohol cue-elicited activation.

METHOD

Participants and procedures

The data for the current study were collected as part of a 2-week randomized controlled clinical trial (ClinicalTrials.gov NCT03489850) of ibudilast for drinking reduction among non-treatment seeking individuals with AUD. All study procedures were approved by the Institutional Review Board of the University of California, Los Angeles. Participants provided written informed consent after discussing study medication with the study physician. The data reported herein were collected from an initial in-person screening visit for all participants, and from a subset ($n = 45$) of these individuals who completed a neuroimaging session on study Day 8.

Participants were men and women between 21- and 50-years old reporting heavy drinking who completed the neuroimaging session after being randomly assigned to receive ibudilast ($n = 20$) or placebo ($n = 25$). Participants were recruited through social media and mass transit advertisements. Interested individuals called the laboratory and completed a phone interview for preliminary eligibility. Likelihood of heavy drinking was initially screened by a score of 2 or higher on the CAGE questionnaire (Ewing, 1984), a mnemonic for questions focused on Cutting down, Annoyance by criticism, Guilty feeling and Eye-openers. In addition, participants also had to meet DSM-5 criteria for current AUD and report drinking at or above heavy drinking criteria (14+ drinks/week for men and 7+ drinks/week for women) over the last 30 days. were: (a) current involvement in treatment programs for alcohol use or have received treatment in the prior 30 days to study participation; (b) use of non-prescription psychoactive drugs or use of prescription medications for recreational purposes; (c) self-reported history of major mental illness (i.e. bipolar disorder or psychotic disorders); (d) current use of antidepressants, mood stabilizers, sedatives, anti-anxiety medications, seizure medications or prescription painkillers; (e) self-reported history of contraindicated medical conditions (e.g. chronic liver disease, cardiac disease); (f) if female, pregnant (as verified by a urine sample), nursing or planning to get pregnant in the next 6 months or refusal to use a reliable method of birth control; (g) breath alcohol concentration >0.000 g/dl as measured by the Dräger Inc. Alcotest® 6510; (h) positive urine toxicology screen for any drug (other than cannabis), as measured by Medimpex United Inc. 10 panel drug test; (i) non-removable ferromagnetic objects in body; (j) claustrophobia and (k) serious head injury or prolonged period of unconsciousness (>30 minutes). Eligible participants were invited to the laboratory to complete an in-person testing battery that included sociodemographic variables, self-report questionnaires and interview-based assessments (described below). Smoking status (categorical; Smoker vs. Non-Smoker) was determined using the first question on The Fagerström Test for Nicotine Dependence (Heatherton *et al.*, 1991), which asks participants if they currently smoke cigarettes.

Measures

Alcohol use and alcohol problems were assessed using (a) the Timeline Follow-back (Sobell and Sobell, 1992) to determine alcohol use quantity and frequency over the past 30 days; (b) the Alcohol Dependence Scale (ADS) (Skinner *et al.*, 1984) and (c) the Alcohol Use Disorder Identification Test (AUDIT) (Saunders *et al.*, 1993) to assess for problems related to excessive drinking and (d) the Obsessive–Compulsive Drinking Scale (OCDS) (Anton *et al.*, 1995) and (e) Penn Alcohol Craving Scale (PACS) (Flannery *et al.*, 1999) to measure alcohol craving. In order to ensure that participants had a current AUD diagnosis, the Structured Clinical Interview for DSM-5 (First *et al.*, 2015) was administered by a master's level clinician to assess for current (i.e. past 12 months) AUD symptoms.

Mood and pain were self-reported using (a) the Beck Depression Inventory II (BDI-II) to capture depressive symptoms over the past 2 weeks, (b) the Pain Catastrophizing Scale (PCS) (Sullivan *et al.*, 1995) that focuses on the emotional experience of physical pain and (c) the Graded Chronic Pain Scale (Von Korff *et al.*, 1992), which is widely used in medical pain research to capture pain severity. However, pain intensity scores were only available for a small subset of the sample ($n = 35$) given that this component of the survey was incorrectly administered in our electronic survey.

Neuroimaging procedures

Neuroimaging took place on a 3.0 T Siemens Prisma Scanner (Siemens Medical Solutions USA, Inc., Malvern, PA) at the UCLA Center for Cognitive Neuroscience. A T2-weighted, high-resolution matched-bandwidth (MBW) anatomical scan (time to repetition [TR] = 5000 ms, time to echo [TE] = 34 ms, flip angle = 90°, voxel size: 1.5 mm × 1.5 × 4 mm, field of view [FOV] = 192 mm^2, 34 slices, ~1.5 minutes) and a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR = 2530 ms, TE = 1.74 ms, time to inversion = 1260 ms, flip angle = 7°, voxel size: 1 mm3, FOV = 256 mm2, ~6.2 minutes) were acquired for co-registration to the functional data. To examine blood oxygen level-dependent signal during the cue-reactivity task, a

Table 1. Demographic and clinical variables for the neuroimaging sample by medication condition

Variable[a]	Placebo ($N = 25$)	Ibudilast ($N = 20$)	Test statistic
Age	31.16 (7.79)	34.40 (9.67)	$t(43) = -1.25$; $P = 0.22$
Sex (male)	15 (33.33%)	13 (28.89%)	χ^2 (1) = 0.12; $P = 0.73$
Cigarette smoker	15 (33.33%)	9 (20.00%)	χ^2 (1) = 1.00; $P = 0.32$
PCS total score	9.40 (8.33)	13.60 (10.36)	$t(43) = -1.51$; $P = 0.14$
Graded Chronic Pain Scale—Pain Intensity Total Score[a]	27.36 (19.92)	21.25 (7.00)	$t(33) = 0.93$; $P = 0.35$
Beck Depression Inventory-II Total Score	**8.64 (7.57)**	**13.95 (8.35)**	$\boldsymbol{t(43) = -2.23}$**;** $\boldsymbol{P = 0.03}$
Timeline follow-back—drinking days	19.96 (6.30)	21.25 (7.00)	$t(43) = -0.65$; $P = 0.52$
Timeline follow—drinks per drinking day	5.44 (3.84)	5.90 (2.72)	$t(43) = -0.44$; $P = 0.66$
Timeline follow—drinks per week	26.92 (26.36)	28.16 (15.46)	$t(43) = -0.19$; $P = 0.85$
AUDIT total score	16.40 (6.25)	16.70 (6.30)	$t(43) = -0.16$; $P = 0.14$
ADS total score	11.40 (6.57)	13.20 (6.59)	$t(43) = -0.91$; $P = 0.37$
OCDS total score	13.28 (7.94)	14.55 (6.15)	$t(43) = -0.59$; $P = 0.56$
PACS total score	11.60 (6.96)	12.50 (5.52)	$t(43) = -0.47$; $P = 0.64$

[a]Measure only available for subsample (Placebo: $N = 19$; Ibudilast: $N = 16$).

T2*-weighted echo planar imaging scan (TR = 2200 ms, TE = 35 ms, flip angle = 90°, FOV = 192 mm, slices = 36, 3.0 mm, ~12 minutes) was also acquired.

Alcohol cue-reactivity task

In a 720 s-long visual alcohol cue-reactivity task (Schacht *et al.*, 2011), participants were presented with 24 pseudo-randomly interspersed blocks of images of alcoholic beverages (ALC), non-alcoholic beverages (BEV), blurred images for visual controls and a fixation cross. Alcoholic beverage images were distributed between beer, wine and liquor (2 blocks of each). Blocks were composed of five images of the same type, presented for 4.8 seconds each, for a total of 24 seconds. Each block was followed by a 6-second washout period during which participants reported their alcohol craving on a 1–4 Likert scale.

Neuroimaging preprocessing

Preprocessing of neuroimaging data followed conventional procedures as implemented in FMRIB Software (FSL v6.0.1 http://www.fmrib.ox.ac.uk/fsl). This included motion correction (Jenkinson *et al.*, 2002), high-pass temporal filtering (100-second cut-off), and smoothing (5-mm full-width, half-maximum Gaussian kernel). Functional and structural data were skull-stripped. Subjects' functional images were registered to their MBW, followed by their MPRAGE using affine linear transformations. Finally, they were normalized to the Montreal Neurological Institute (MNI) 152-brain-average template through non-linear registration (Andersson *et al.*, 2007). All functional magnetic resonance imaging (fMRI) data had been used in previous studies (Grodin *et al.*, 2021; Burnette *et al.*, 2021a; Burnette *et al.*, 2021b), and as such, met criteria for quality control (exclusion criteria: >2 mm translational displacement, >1.5° rotation). No participants or images were excluded for quality control or motion issues as part of this study.

Data analysis

Group differences on demographic and clinical variables between the placebo and ibudilast groups were tested using *t*-tests for continuous outcomes and chi-square (χ^2) tests for categorical outcomes. The primary contrast of interest, ALC > BEV, was defined in first-level models. FSL's Featquery tool was used to extract mean percent signal change for all subjects from *a priori* striatal regions of interest (ROIs). The first ROI, bilateral VS, was defined anatomically as the nucleus accumbens using the Harvard–Oxford subcortical structure probability atlas and binarized at a 0.5 probability threshold (Kaag *et al.*, 2019; Ray *et al.*, 2014). The bilateral DS ROI was defined anatomically as the caudate and putamen from the Harvard–Oxford atlas used above, also binarized at a 0.5 probability threshold. Overlap between the VS and DS regions were subtracted from the DS mask to distinguish between dorsal and ventral striatal areas (Kaag *et al.*, 2019; Liu *et al.*, 2017). Pearson correlation coefficients were calculated to examine zero-order associations between pain, alcohol, and neural activation to alcohol cues. Multiple linear regression analyses were used to examine the relationship between pain catastrophizing and alcohol cue-reactivity in the VS and DS. In these analyses, demographic variables, depressive symptomatology, smoking status, alcohol use and medication were used as statistical controls. Predictor variables were mean-centered in regression analyses. Alcohol use was included as a covariate because baseline alcohol drinking levels may influence reactivity to alcohol cues in the scanner and is also associated with pain catastrophizing (Table 2). A two-level regression model (Level 1: Subjects, Level 2: Brain region (DS vs. VS) was used to test whether the PCS total score standardized estimates for dorsal and striatal activation were significantly different from each other. Student's *t*-tests, Pearson correlations and regression analyses were conducted using SAS 9.4. Statistical significance was set at $P < 0.05$.

An exploratory whole-brain general linear model was conducted to assess the relationship between PCS total score and neural alcohol cue reactivity across all subjects. Medication group (ibudilast or placebo), age, sex and smoking status (smoker vs. non-smoker) 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).

RESULTS

Sample demographics

Sample demographics and clinical characteristics by medication for the neuroimaging sample ($n = 45$) have been previously reported in (Burnette *et al.*, 2021a). Table 1 includes sample characteristics by medication condition for measures relevant to the current study. While participants

Table 2. Pearson correlations between pain catastrophizing, pain intensity, alcohol variables and neural alcohol cue-elicited activation

	1	2	3	4	5	6	7	8	9	10
1. PCS total score	1.00									
2. Pain intensity total score[a]	**0.34***	1.00								
3. Drinks per drinking day	-0.04	-0.02	1.00							
4. Drinks per week	0.08	-0.15	**0.87*****	1.00						
5. AUDIT total score	**0.31***	0.09	**0.60*****	**0.67*****	1.00					
6. ADS total score	**0.33***	0.12	**0.51*****	**0.49*****	**0.81*****	1.00				
7. OCDS Scale total score	**0.41****	0.07	**0.42****	**0.58*****	**0.72*****	**0.61*****	1.00			
8. PACS total score	**0.35***	0.02	**0.58*****	**0.64*****	**0.76*****	**0.71*****	**0.81*****	1.00		
9. Ventral striatum activation	-0.05	-0.11	-0.01	-0.02	0.003	0.06	-0.04	-0.02	1.00	
10. DS activation	**0.26***	0.17	0.03	0.12	0.17	0.04	0.29	0.12	0.24	1.00

[a]Graded Chronic Pain Scale was only available for a subsample (Placebo: $N = 19$; Ibudilast: $N = 16$). * indicates a significant association at $P < 0.05$. ** indicates a significant association at $P < 0.01$. *** indicates a significant association at $P < 0.001$.

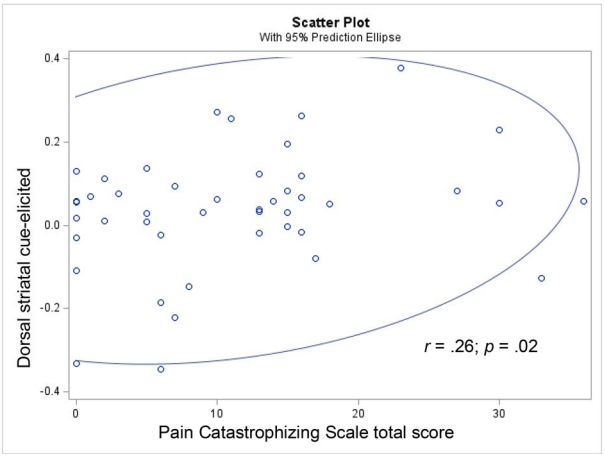

Fig. 1. Scatter plot of the relationship between pain catastrophizing and alcohol cue-elicited activation in the DS.

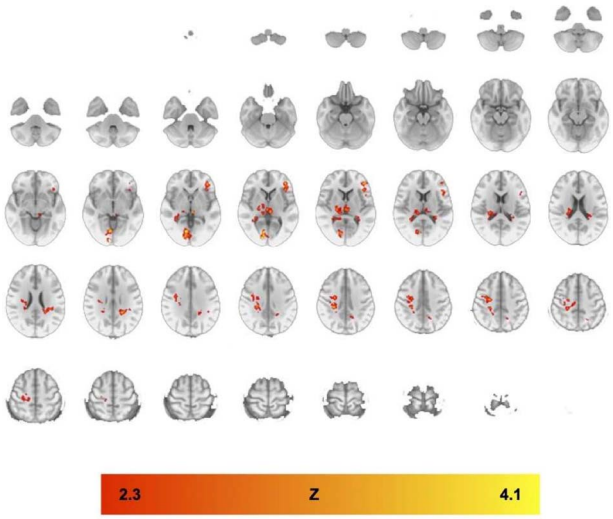

Fig. 2. Pain catastrophizing whole-brain analysis clusters. Regions in which pain catastrophizing were significantly correlated with neural cue-reactivity in the ALC > BEV contrast (see Table 3 for list of clusters). Color bar represents z-values. Whole-brain results are thresholded at z > 2.3, cluster-forming threshold of $P < 0.05$. Brain maps are displayed in radiological convention (right = left), and all coordinates are in MNI space.

in the placebo ($n = 25$) and ibudilast ($n = 20$) groups did not differ on several measures included in the current study, participants in the ibudilast group had significantly higher BDI-II total scores compared with participants in the placebo group, $t(43) = -2.23$; $P = 0.03$ (Table 1).

Correlation analyses

Zero-order Pearson's correlations among pain, alcohol use and neural cue-elicited activation are shown in Table 2. PCS total score was significantly associated with chronic pain intensity ($P = 0.04$), AUDIT total score ($P = 0.04$), ADS total score ($P = 0.03$), OCDS total score ($P = 0.004$), PACS total score ($P = 0.02$) and DS activation ($P = 0.02$). Chronic pain intensity was not significantly associated with any alcohol variable or neural cue-elicited activation. Figure 1 shows a scatter plot of the relationship between PCS total scores and alcohol cue-elicited activation in the DS without controlling for the influence of any other variables.

VS/DS ROI neuroimaging results

PCS total score was significantly associated with greater alcohol cue-elicited activation in the DS controlling for medication and other variables in the model [$b = 0.006$; standard error (SE) = 0.003; $t = 2.19$; $P = 0.03$]. No other variables in the model were significantly associated with alcohol cue-elicited dorsal striatal activity (P's > 0.05). The intercept for this model was 0.081 (SE = 0.047). PCS total score was not significantly associated with alcohol cue-elicited ventral striatal activation controlling for other variables in the model ($b = 0.001$; SE = 0.005; $t = 0.23$; $P = 0.73$). Additionally, no other variables in the model were associated with alcohol cue-elicited ventral striatal activation (P's > 0.05). The intercept for this model was 0.026 (SE = 0.084). The standardized slopes for PCS total score on neural activation were significantly different such that the slope was steeper in the DS compared with the VS [PCS total score X Brain Region interaction; $\beta = 0.34$, SE = 0.20, $t(43) = 1.79$; $P = 0.02$].

Exploratory whole-brain neuroimaging results

PCS total score was positively associated with neural activation to alcohol cues in regions including the bilateral thalamus, left precuneus and left frontal pole (Fig. 2 and Table 3) across both groups, controlling for medication, age, sex and smoking status. Whole-brain results are thresholded at whole-brain results are thresholded at z > 2.3, cluster-forming threshold of $P < 0.05$. No regions showed a significant negative association between activation and PCS total score in whole-brain analysis.

Table 3. Clusters with significant association between pain catastrophizing and the ALC > BEV contrast, across groups. Z-statistic maps were thresholded using cluster-corrected statistics with a height-threshold of Z > 2.3 and cluster-forming threshold of $P < 0.05$. Coordinates are listed in MNI space

Brain Region	Cluster voxels	Max Z-statistic	*x*	*y*	*z*
Activation during Alc > Bev contrast correlated with pain catastrophizing					
R postcentral gyrus	1753	3.79	28	−30	38
L thalamus		3.66	−4	−26	2
R thalamus		3.42	22	−18	6
R hippocampus		3.34	30	−40	4
R precentral gyrus		3.34	28	−12	48
R intracalcarine gyrus	503	3.9	16	−84	2
R lingual gyrus		3.57	6	−70	−4
R occipital pole		3.33	12	−92	−4
L opercular cortex	402	3.38	−36	−36	24
L precuneus		2.97	−14	−54	40
L frontal pole	397	3.71	−44	42	8
L inferior frontal gyrus		3.18	−46	24	12

DISCUSSION

Despite evidence demonstrating pain catastrophizing as a predictor of substance and alcohol problems, no studies have examined pain catastrophizing and alcohol cue-induced neural activity in addiction-relevant brain regions, namely the VS and DS. In this study of non-treatment-seeking individuals with AUD, we examined whether pain catastrophizing would predict greater alcohol cue-induced neural activation in the DS compared with the VS. An additional goal was to conduct an exploratory whole-brain analysis to further investigate associations between pain catastrophizing and alcohol cue-elicited brain responses in heavy drinkers. We found that pain catastrophizing predicted greater cue-induced neural activation in the DS but not VS. The whole-brain analysis revealed that pain catastrophizing was associated with cue-induced neural activation in the bilateral thalamus, left precuneus and left frontal poles. Taken together, these results begin to elucidate the mechanism by which psychological pain constructs, such as pain catastrophizing, may contribute to problematic alcohol use.

The findings from the current study showed that pain catastrophizing predicted greater cue-induced neural activation in the DS but not VS. These results are in line with our hypothesis given previous work from our laboratory showing that pain catastrophizing is associated with self-reported heavy drinking to feel normal rather than for alcohol's reinforcing effects in heavy drinkers (Nieto *et al*., 2020). These findings are also consistent with current addiction theories, namely the allostatic (Koob and Schulkin, 2019) and incentive salience models (Robinson and Berridge, 1993). According to these theories, initial alcohol use is characterized by and positive reinforcement (i.e. drinking because of alcohol's rewarding effects) and 'liking', behaviors that are mediated by the VS (Burton *et al*., 2015). For the subset of individuals who develop AUD, there is a transition from positive to negative reinforcement (i.e. drink to alleviate negative emotional states) and 'wanting', wherein alcohol use becomes more compulsive and habitual, behaviors mediated by the DS (Burton *et al*., 2015). That pain catastrophizing predicted greater cue-induced neural activation in the DS likely indicates that a sizeable portion of our sample of individuals with AUD may be using alcohol to cope or alleviate negative affective states. In agreement with this perspective, pain catastrophizing is associated with depressive symptomatology in heavy drinkers (Nieto *et al*., 2020) and greater anxiety symptoms and more days of mood disturbances controlling for pain severity among individuals seeking treatment for substance use disorders who also have co-occurring pain (Kneeland *et al*., 2019). Thus, pain catastrophizing may be a key factor escalating substance and alcohol use in order to alleviate these negative states.

Our exploratory whole-brain analysis revealed that pain catastrophizing is associated with cue-induced neural activation in the bilateral thalamus, left precuneus and left frontal poles. Compared with the VS and DS, the thalamus has not been extensively studied in addiction research. However, there is accumulating evidence demonstrating lower thalamic gray matter volume is associated with shorter length of abstinence from alcohol (Durazzo *et al*., 2015; Yang *et al*., 2016), and reduced metabolism and functional connectivity with striatal and frontal regions at rest in individuals with AUD (Chanraud *et al*., 2007; Mon *et al*., 2014; Huang *et al*., 2018). There is evidence that drug cues in abstinent heroin users produced changes in the functional coupling between the bilateral thalamus and prefrontal cortex, which was correlated with craving (Liu *et al*., 2021) . Despite lower thalamic baseline activity, exposure to alcohol cues results in increased activation in the thalamus (Feldstein Ewing *et al*., 2010). Our results indicate that pain catastrophizing may enhance thalamic cue-reactivity in individuals with AUD. Indeed, pain-related threats or pain catastrophizing produced greater bilateral thalamic activity in fibromyalgia subjects (Gracely *et al*., 2004; Sandström *et al*., 2020). Pain catastrophizing is also associated with cue-induced activity in the precuneus, a region of the parietal lobe. The precuneus has been implicated in drug and alcohol cue-reactivity studies (Engelmann *et al*., 2012; Schacht *et al*., 2013; Courtney *et al*., 2014). The precuneus, in conjunction with other brain regions, is part of a large network that integrates and relays cue information from the visual system to systems involved in motivated behavior and choice (Engelmann *et al*., 2012). There is a positive relationship between subjective craving for alcohol and cue-induced precuneus activation (Tapert *et al*., 2003; Park *et al*., 2007) in individuals with AUD. In light of these findings and our previous work demonstrating that pain catastrophizing predicts tonic alcohol craving, it may be the case that pain catastrophizing heightens alcohol

craving via activation of the precuneus among individuals with AUD.

These findings should be interpreted in light of the study's strengths and limitations. One notable strength is that this study includes a novel combination of clinical phenotyping and neuroimaging methods. Limitations include a modest sample size, lack of multiple comparisons correction, narrow age range and that our study excluded individuals taking prescription opioids and the lack of moderate/severe pain severity and pain-related disability in the sample. That is, these findings may not generalize to heavy drinkers with AUD who co-use prescription opioids to manage pain. This study was conducted as part of a larger medication trial; thus, replication in studies without a medication component is necessary. Additionally, future work should include laboratory pain paradigms to more directly investigate the relationship between psychological pain constructs and underlying neural circuits involved in alcohol craving.

Overall, the current study identifies pain catastrophizing as a predictor of alcohol cue-elicited activation in the DS, an addiction-relevant brain region associated with compulsive and habitual behaviors, among individuals with AUD. This represents a promising area to target treatment as pain catastrophizing can be reduced using behavioral interventions, such as cognitive behavioral therapy or transcranial magnetic stimulation. Additionally, whole-brain analyses revealed novel brain regions wherein pain catastrophizing was associated with cue-elicited activation. These results extend previous work highlighting the predictive utility of pain catastrophizing on alcohol craving and suggest a neural mechanism by which pain catastrophizing may be influencing cue-induced craving in heavy drinkers with AUD.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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