Cue-elicited craving, thalamic activity, and physiological arousal in adult non-dependent drinkers

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ABSTRACT

Changes in physiological arousal frequently accompany cognitive and affective challenges. Many studies employed cue exposure paradigms to investigate the neural processes underlying cue-elicited drug and alcohol craving. However, whether cue-elicited craving relates to changes in physiological arousal and the neural bases underlying the potential relationship remain unclear. Here we examined cerebral cue-related activations in relation to differences in skin conductance responses (SCR) recorded during alcohol vs. neutral cue blocks in 61 non-dependent alcohol drinkers (30 men). Imaging and skin conductance data were collected and processed with published routines. Mediation analyses were conducted to examine the inter-relationship between regional activities, cue-elicited craving, and SCR. The results showed higher SCR during alcohol than during neutral cue exposure. Despite no differences in drinking characteristics, men as compared to women demonstrated higher craving rating, and men but not women demonstrated a positive correlation between alcohol (vs. neutral) cue-evoked craving and SCR. Further, across subjects, thalamic cue activity was positively correlated with differences in SCR between alcohol and neutral cue blocks in men but not in women. Mediation analyses suggested that thalamic activity mediated the correlation between craving and SCR across men and women, and in men but not women alone. These findings substantiate physiological and neural correlates of alcohol cue response and suggest important sex differences in the physiological and neural processes of cue evoked craving. Centered on the intralaminar and mediodorsal subregions, the thalamic correlate may represent a neural target for behavioral or pharmacological therapy to decrease cue-elicited arousal and craving.

1. Introduction

Skin conductance response (SCR) is a physiological index of arousal. Via sympathetic innervations of the skin sweat glands, heightened arousal is associated with increases in electrodermal conductance (Critchley, 2002; Naqvi and Bechara, 2006). The SCR can be elicited by effort, environmental stimuli, and/or emotional challenges.

Craving for abused substances is known to be associated with changes in interoceptive responses and physiological arousal (Buckner et al., 2016; Carter et al., 2009; Childress et al., 1988; Fox et al., 2012; Li et al., 2015; Pachas et al., 2015; Robbins et al., 2000; Sinha et al., 2009; Trotzke et al., 2014; Zhao et al., 2012). Many studies have employed functional brain imaging to investigate the neural correlates of craving (see (Jasinska et al., 2014) for a review) and those underlying changes in physiological arousal in response to cognitive and affective

demands (Critchley et al., 2011). For instance, compared to controls, individuals with alcohol use disorders demonstrated greater alcohol cue-related activation of parietal and temporal regions, including the posterior cingulate, precuneus and superior temporal gyrus (Schacht et al., 2013). We recently demonstrated higher responses to alcohol vs. neutral cues in the occipital, retrosplenial, and medial orbitofrontal cortex as well as left caudate head in non-dependent drinkers (Zhornitsky et al., 2018). Changes in physiological arousal engages a wide swath of cortical and subcortical regions, including the insula and medial prefrontal cortex (Critchley, 2002; Zhang et al., 2012). In particular, the ventromedial prefrontal cortex appears to play a specific role in regulating physiological arousal (Nagai et al., 2004; Zhang et al., 2013). On the other hand, no imaging studies have examined the neural processes underpinning cue-elicited changes in arousal, whether the regional responses correspond to cue-elicited activities, or how these

neural activities relate to cue-elicited craving.

Women and men exhibited differences in cue evoked changes in craving, physiological and neuroendocrine responses, and other neurobiological processes that underlie the development of alcohol addiction (Barker and Taylor, 2017; Ceylan-Isik et al., 2010). Alcohol-associated stimuli induced craving in male but not female social drinkers (Willner et al., 1998). Male as compared to female binge drinkers showed more significantly elevated cue reactivity in event-related electric potentials (Petit et al., 2013). In social drinking males but not females, craving was associated with alcohol cue-induced striatal activation (Seo et al., 2011). A more recent study showed that, while inducing similar levels of self-reported craving, exposure to visual alcohol cues led to significantly stronger striatal activation in male compared to female drinkers (Kaag et al., 2018). On the other hand, an earlier work suggested no sex differences in cue reactivity in dependent alcohol drinkers (Rubonis et al., 1994). Together, these studies suggest the importance to consider sex differences in alcohol cue reactivity.

Here, sixty-one non-dependent drinkers participated in clinical assessments and an fMRI study of alcohol cue reactivity in conjunction with recordings of skin conductance activity. We addressed several issues. First, is alcohol cue-elicited subjective craving related to changes in physiological arousal? Second, what are the neural processes underlying cue-elicited changes in physiological arousal? Third, do male and female drinkers differ in cue-elicited changes in arousal and in the neural processes underlying the changes in arousal?

2. Materials and methods

2.1. Subjects, assessments and behavioral tasks

Candidates were recruited from the greater New Haven, CT area. Sixty-one non-dependent adult drinkers met eligibility and participated in this study, including 51 of the 61 participants (Zhornitsky et al., 2018) who were scanned with concurrent recording of skin conductance, and 10 new participants (Table 1). All subjects were required to be physically healthy with no major medical conditions. Those with current use of prescription medications or with a history of head injury or neurological illness were excluded. Other exclusion criteria included current or past dependence on a psychoactive substance (except nicotine) and current or history of Axis I disorders according to the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Candidates who reported current use of illicit substances or tested positive for cocaine, methamphetamine, opioids, marijuana, barbiturates, or benzodiazepines were not invited to participate. The Human Investigation committee at Yale University School of Medicine approved the study procedures. All participants signed an informed consent prior to the study.

Participants were evaluated with Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001), an instrument widely used to assess alcohol use behavior and related problems. Participants were also evaluated with the Alcohol Expectancy Questionnaire or AEQ-3 (George et al., 1995). The AEQ-3 consists of 40 items to assess both positive (6 subscales) and negative (2 subscales) alcohol expectancy. Although the expectancy subcomponents are statistically discernible, the subscales are highly inter-correlated (George et al., 1995). Here, we used the global positive (GP) subscale (five items, with score from 5 to 30) to reflect positive alcohol expectancy. Participants were also assessed with the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991) and averaged 0.7 ± 1.9 (mean ± SD) in FTND score, suggesting low dependence.

2.2. Behavioral tasks

We employed a cue-induced alcohol craving task in the current study. Participants viewed alcohol-related or neutral pictures and reported alcohol craving in alternating blocks. Briefly, a cross was used to engage attention at the beginning of each block. After 2 s, six pictures displaying alcohol related cues (alcohol block) or neutral visual scenes (neutral block) were shown for 6 s each. Participants were asked to view the pictures and ponder how they might relate to the scenes. The pictures were collected from the Internet and independently reviewed by two investigators. Alcohol pictures included bar scenes, individuals or a group of people (both men and women) holding or drinking alcoholic beverages, and images of a variety of alcoholic drinks, such as beer, wine, and vodka. Neutral pictures comprised natural sceneries. Participants were asked at the end of each block to report how much they craved for alcohol from 0 (no craving) to 10 (highest craving ever experienced) on a visual analog scale. Each block lasted about 45 s, including time for craving rating. A total of 6 alcohol and 6 neutral blocks took approximately 9 m to complete. Each participant completed two runs of the task.

2.3. Skin conductance acquisition and analysis

We recorded skin conductance continuously during fMRI from the palmer surfaces of the index and middle fingers of the left hand with a Biopac MP150 system. The system employed a AcqKnowledge 4.1 software (Biopac Systems, USA) and the electrodermal activity amplifier module (Galvanic Skin Response [GSR] 100c) set at a channel sampling rate of 31 Hz and a gain of 5 μSiemens (μS) per volt (0.0015 μS resolution). Recording was synchronized with behavioral task and image acquisition. We applied a smoothing function (moving average of 500 ms) to eliminate high-frequency noise (Figner and Murphy, 2011), and computed the skin conductance response (SCR) to alcohol and neutral cues by subtracting the baseline, defined as the signal at time = 0 s, from the level of skin conductance over the entire 36 s (6 picture cues each presented for 6 s) (Figner and Murphy, 2011; Gamer et al., 2007; Schiller et al., 2008; Spoormaker et al., 2011).

2.4. Imaging protocol and data analyses

Imaging protocol and data pre-processing followed publishd routines, as described in the Supplement.

In modeling of imaging data, we distinguished alcohol and neutral cue blocks for each individual subject using a general linear model (GLM) that included the realignment parameters in all six dimensions. We corrected for serial autocorrelation caused by aliased cardiovascular and respiratory effects by a first-degree autoregressive model. The GLM was used to estimate the component of variance explained by each of the regressors. We constructed for individual subjects a contrast of alcohol vs. neutral blocks to evaluate regional activities that differentiated viewing of alcohol and neutral pictures. We used the contrast or *con* (difference in β) images of the subject-level analysis for group-level statistical (random-effects) analyses. We performed a one-sample

Table 1
Demographics and drinking measures of male and female participants.

Subject characteristic	Men (n = 30)	Women (n = 31)	P value*
Age (yrs)	32.8 ± 11.6	35.7 ± 14.2	0.39
AUDIT score	10.0 ± 10.6	8.7 ± 9.3	0.61
Duration of alcohol use (yrs)	14.4 ± 11.3	17.0 ± 14.7	0.36
# of drinking days/mo, prior yr	8.4 ± 5.9	9.0 ± 5.6	0.67
# of drinks/per occasion	3.5 ± 2.5	3.1 ± 2.3	0.51
# of drinks/mo, prior yr	34.1 ± 43.0	32.8 ± 40.4	0.90
GP score	12.7 ± 5.7	13.5 ± 6.2	0.64
FTND score	0.4 ± 1.5	1.0 ± 2.3	0.22
Current smoker (yes/no)	4/25[§]	10/21	0.09

Note: values are mean ± S.D.; *two-tailed two-sample *t*-test, except for smoker status which was based on Chi-square test; AUDIT: Alcohol Use Disorder Identification Test; GP: global positive subscore of the Alcohol Expectancy Questionnaire-3; FTND: Fagerström Test for Nicotine Dependence. [§]One subject's data missing.

t-test to identify regional response to alcohol *vs.* neural cues across subjects. We also performed a linear regression of *con* images against the differences in SCR to alcohol *vs.* neutral cues across subjects, with age as a covariate. Following current reporting standards, we evaluated the results with voxel p < 0.001, uncorrected, in combination with cluster p < 0.05, FWE corrected, on the basis of Gaussian random field theory, as implemented in SPM. For clusters comprising many distinct regions, we employed a higher threshold (p < 0.0001, uncorrected or p < 0.05 FWE corrected) to distinguish the individual peaks. In region of interest (ROI) analysis, we used MarsBaR (http://marsbar. sourceforge.net/) to derive for each individual subject the β contrast or cue-elicited activity for the ROIs. We defined functional ROIs from clusters of whole brain analysis, and showed all voxel activations in the Montreal Neurological Institute (MNI) coordinates.

2.5. Mediation analyses

We performed mediation analyses as described in the Supplement.

3. Results

3.1. Cue-elicited craving

Subjects reported higher craving during alcohol (3.0 ± 2.4) as compared to neutral (1.9 ± 2.0) cue blocks (t = 7.13, p < 0.001, paired sample *t*-test). Men as compared to women showed greater difference in subjective rating of alcohol (vs. neutral) cue evoked craving (men: 1.5 ± 1.4; women: 0.8 ± 0.9; t = 2.22, p = 0.0300, two-sample *t*-test).

3.2. Skin conductance responses

Skin conductance responses during alcohol and neutral cue blocks are shown in Fig. 1. The SCR maintained a similar level during alcohol cue but gradually decreased over the neutral cue blocks. We compared the SCR between blocks for the entire 36 s. The difference in SCR between alcohol and neutral cue blocks was significant across participants (t = 2.16, p = 0.0349, two-tailed paired sample *t*-test). Although the mean of SCR difference was numerically higher in men (0.1219 ± 0.3905 μS) than women (0.0406 ± 0.1386 μS), a direct comparison failed to demonstrate differences in men vs. women (t = 1.09, p = 0.2804; two-tailed two-sample *t*-test).

We also examined the correlation of SCR (alcohol – neutral) and cue-elicited craving (alcohol – neutral) across subjects. Linear regression showed a positive correlation in men and women combined (r = 0.36, p = 0.0043) and in men (r = 0.41, p = 0.0231), but not in women (r = 0.01, p = 0.9753) alone.

Across subjects, the AUDIT score was not correlated with cue-induced craving in men and women combined (r = 0.02, p = 0.8585), or in men (r = −0.15, p = 0.4277) or women (r = 0.27, p = 0.1418) alone. The AUDIT score was also not correlated with differences in SCR between the alcohol and neutral cue blocks in men and women combined (r = −0.03, p = 0.8006), in men (r = −0.09, p = 0.6395) or in women (r = 0.09, p = 0.6410) alone.

GP score was positively correlated with the difference in craving rating between alcohol and neutral cue blocks for men and women combined (r = 0.33, p = 0.0090), for men (r = 0.44, p = 0.0160), but not for women (r = 0.29, p = 0.1081). GP score was not correlated with SCR (alcohol - neutral) in men and women combined (r = 0.09, p = 0.4829), or in men (r = 0.08, r = 0.6758) or women (r = 0.20, p = 0.2745) separately.

3.3. Regional responses to alcohol vs. neutral cues

We first conducted a two-sample *t*-test both with and without age as a covariate and observed that men and women did not show significant differences in regional responses to alcohol *vs.* neutral cues, at p < 0.001, uncorrected. Thus, we combined men and women in examining cue-elicited regional responses. One-sample *t*-test showed higher activities in response to alcohol *vs.* neutral cues in bilateral occipital cortices and bilateral but predominantly left-hemispheric ventromedial prefrontal and frontopolar cortices. Neural as compared to alcohol cues engaged higher activity in the cuneus/precuneus, mid-cingulate cortex/supplementary motor area, right inferior parietal cortex, and bilateral middle/superior temporal gyrus that involved the posterior insula and superior parietal lobule (Fig. 2A). Regions meeting cluster p < 0.05 FWE are summarized in Table 2.

3.4. Cue-elicited responses (alcohol vs. neutral) in relation to SCR

There was a total of 10 clusters identified from the one-sample *t*-test of alcohol vs. neutral cue response (Table 2). In regions of interest (ROI) analyses, we extracted the β contrast for each cluster for a correlation with SCR (alcohol – neutral) and examined the results at a corrected p < 0.005 (0.05/10). The results of linear regressions showed that cue-elicited activation of the ventromedial prefrontal cortex (vmPFC; x = −6, y = 44, z = −11) was significantly correlated with the difference in SCR between alcohol and neutral cue blocks (r = 0.38, p = 0.0022).

In addition to ROI analyses, we also conducted a whole-brain analysis with linear regression of the contrast (alcohol – neutral) against differences in SCR (alcohol – neutral, over the 36-s period) with age as a covariate. The results showed higher activities in a larger cluster encompassing subregions of the thalamus and the body of the caudate nucleus, as well as a small cluster in the cerebellum. Using a more stringent threshold of p < 0.0001, uncorrected and cluster p < 0.05 FWE-corrected, we identified three distinct clusters, including the left ventroposterior lateral thalamus (x = −21, y = −22, z = 22, voxel Z = 4.74, 26 voxels); right ventroposterior lateral thalamus (x = 30, y = −28, z = 7, voxel Z = 4.66, 60 voxels); and intralaminar/mediosorsal thalamus (x = −6, y = −10, z = 4, voxel Z = 4.32, 37 voxels; shown in an inset of coronal sections, too) (Fig. 2B). We extracted the beta contrast (alcohol – neutral) of a region of interest (ROI) combining all three clusters (ROI_3) and another ROI comprising solely the intralaminar/mediodorsal thalamus (ROI_1) for correlation and mediation analyses.

We examined the relationship between thalamic and vmPFC cue response and skin conductance response to alcohol vs. neutral cues for men and women separately to examine potential sex differences. The results showed that for both ROI_3 and ROI_1, thalamic cue response was significantly correlated with the SCR for men but not for women. A slope test confirmed the sex differences for ROI_3 (z = 1.86, p = 0.0314, one-tailed); and for ROI_1 (z = 2.12, p = 0.017, one-tailed). VmPFC cue response was positively correlated with SCR both in men (r = 0.44, p = 0.0140) and in women (r = 0.36, p = 0.0440). A slope test showed that the correlation did not differ significantly between men and women (z = 0.35, p = 0.7263). These results are shown in Fig. 3.

3.5. Cue-elicited responses (alcohol vs. neutral) in relation to craving rating

We also evaluated the neural correlates of inter-subject variation in cue-elicited craving in a whole-brain linear regression [i.e., with craving rating (alcohol – neutral cue) as the regressor]. At he same threshold of voxel p < 0.001, uncorrected, the regression did not reveal any voxels in correlation with craving rating.

3.6. Mediation analysis

Subjective craving, thalamic/vmPFC cue response, and SCR were pair-wise positively correlated. Thus, we examined the inter-relationships using mediation analyses for men and women combined and for
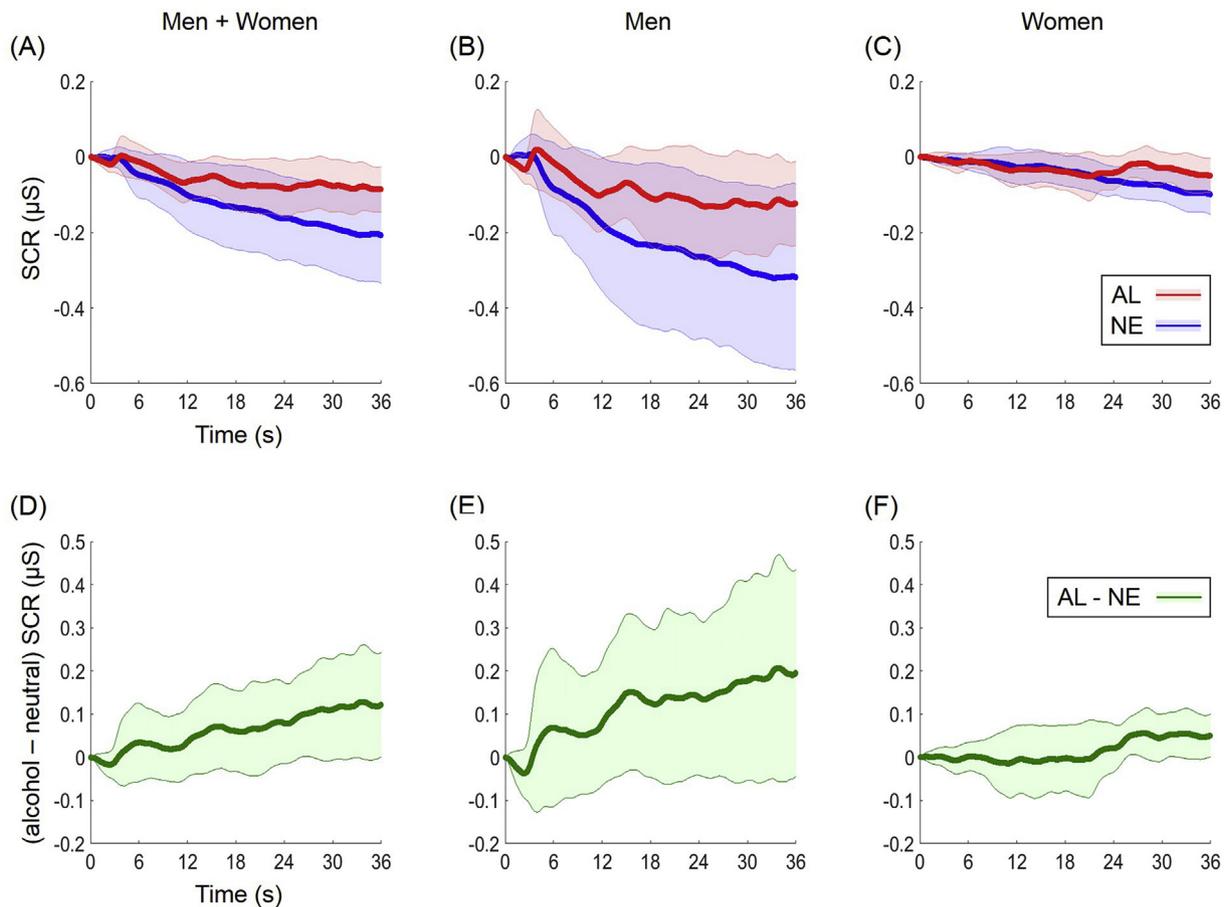
Fig. 1. Skin conduct response (SCR) to alcohol (AL) and neutral (NE) cues. **(A–C)** The mean (line) and 95% confidence interval (shade) of alcohol (red) and neutral (blue) cue evoked SCRs. **(D–F)** The mean and 95% confidence interval of the difference in SCR (green): "alcohol minus neutral." The data are shown for men and women combined (A, D), men (B, E), and women (C, F). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

men alone. The findings of significant mediation are shown in Fig. 4. For both ROI_3 and ROI_1, thalamic cue response mediated the correlation between cue-elicited craving and changes in SCR. None of the other five models showed significant mediation. For the vmPFC, no models showed significant mediation, although, as with the thalamus, the model craving - > neural activity - > SCR demonstrated the best p values, which were nearly significant (p = 0.053 for men and women combined; p = 0.112 for men). The results of all mediation analyses are shown in the **Supplement**.

4. Discussion

The current results showed that alcohol drinkers habituated to neutral but not to alcohol cues (Laberg et al., 1992) and, as a result, demonstrated higher skin conductance response (SCR) during alcohol vs. neutral cue exposure. These differences in cue evoked SCRs appeared to be carried largely by men, although a direct comparison failed to show significant sex differences. Further, the differences in SCR to alcohol vs. neutral cues were related to distinct regional responses in the thalamus, in men and women combined and in men but not women alone. Mediation analysis suggested that thalamic cue response mediated the relationship between cue induced craving and physiological reactivity. Together, these findings support a role of the thalamus in cue-elicited alcohol craving and increases in physiological arousal.

4.1. Thalamic responses to physiological arousal during cue exposure

Many cortical and subcortical regions respond to increases in physiological arousal during cognitive and emotional challenges and some of the regions respond specifically to task manipulations or psychological states. For instance, during biofeedback relaxation, anterior cingulate, amygdala, and insula activity was modulated by task manipulations that increased interoceptive processing, while variation in anterior insula activity reflected an interaction between accuracy and sensitivity of feedback (Critchley et al., 2002). In a study of the guilty knowledge test to examine the neural processes underlying deception, SCR amplitudes were linearly related to activity in the cerebellum, the right inferior frontal cortex, and the supplementary motor area (Gamer et al., 2007). A study of pain responses revealed brain activation more specifically associated with the SCR in the supracallosal ACC, amygdala, thalamus, and hypothalamus, distinct from regional activations to pain (Dube et al., 2009). Another study combined fMRI and measurements of electrodermal responses during an effortful motor task (MacIntosh et al., 2007). In addition to conventional hemodynamic modeling, skin conductance data have also used as time series to generate activation images from fMRI data. Whereas standard hemodynamic model demonstrated activities in the insula and cingulate cortices, modeling with skin conductance waveforms revealed additional activities in pre- and postcentral gyri, putamen and parietal cortices. Together, these studies suggest that the regional activities underlying SCR modulation may be task-dependent, likely because physiological arousal varies to task demands and are not readily separable from these manipulations and behaviors. In fact, some studies employed SCR to
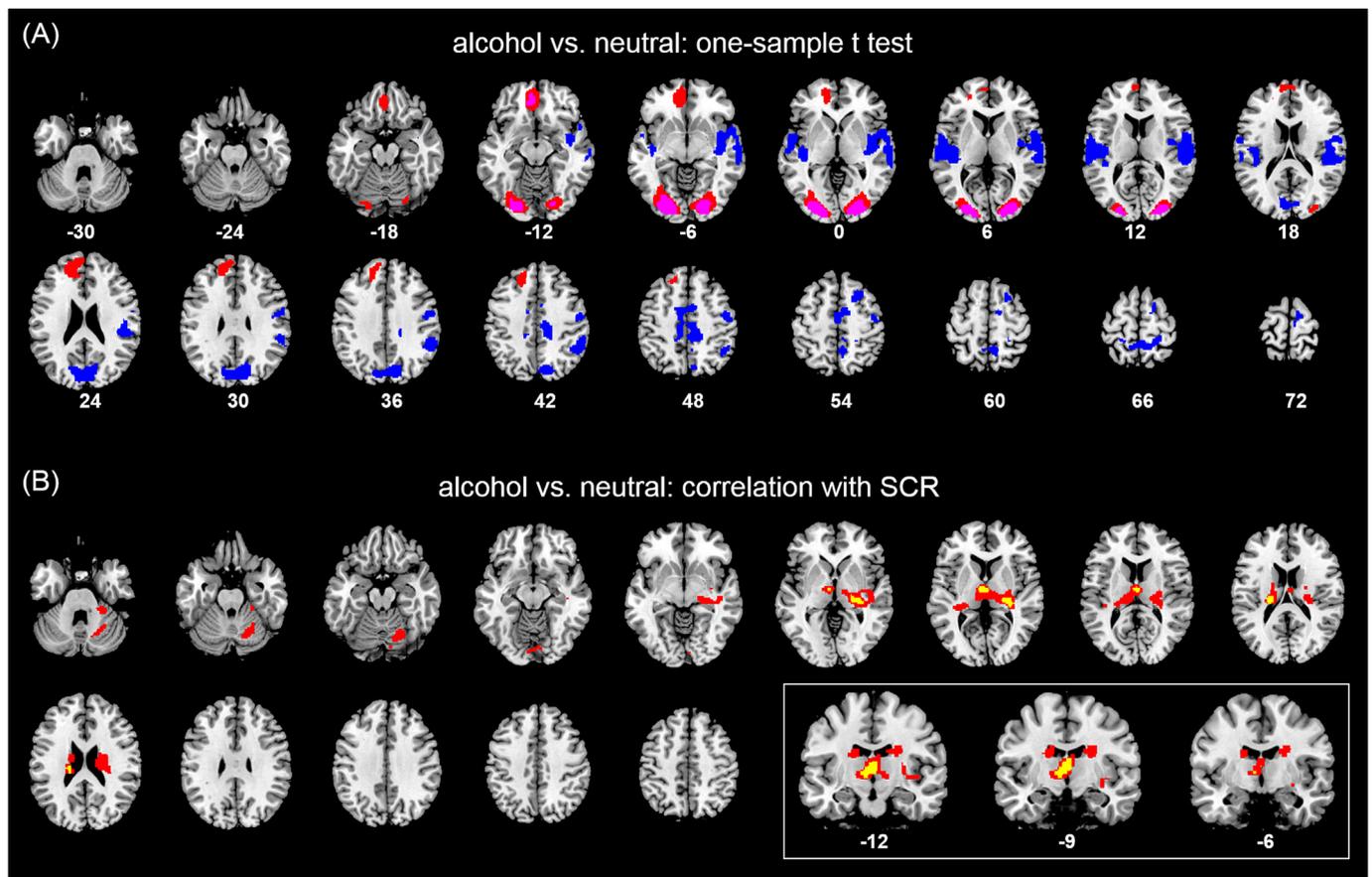
Fig. 2. (A) Regional activations to alcohol vs. neutral cues (one sample *t*-test). Red and blue color indicates clusters obtained of alcohol > neutral and neutral > alcohol, respectively, at voxel p = 0.001, uncorrected. Pink color shows clusters with a voxel peak meeting p < 0.05, FWE-corrected, for the contrast alcohol > neutral. **(B)** Regional activations to alcohol vs. neutral cues in positive correlation with SCR (alcohol – neutral) in a linear regression, shown in the same axial sections. Clusters in red were obtained with voxel p < 0.001, uncorrected and those in yellow with voxel p < 0.0001, uncorrected. We used the latter, more stringent threshold in order to better visualize the locations of peak activities. Neurological orientation: right = right. The three coronal sections in the inset highlight the intralaminar and mediodorsal thalamus. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Regional activations to alcohol vs. neutral cues, one-sample *t*-test.

| Region	Cluster	Voxel	MNI Coordinates (mm)		
	Size (voxels)	Z Value	X	Y	Z
L OC*	288	6.64	−18	−94	4
R OC*	245	6.30	21	−91	4
L vmPFC/FPC*	40	5.20	−6	44	−11
R Cu/PCu	432	−4.70	9	−76	31
R MTG/STG/PI/IPC	1085	−4.45	42	−16	−5
L MTG/STG/PI	520	−4.44	−60	−28	13
L/R SPL	164	−4.30	9	−49	67
R PCG	137	−4.05	48	−10	52
R/L mCG/SMA	337	−4.01	15	−34	46
R SFG	105	−3.93	24	14	55

Note: L: left; R: right. OC: occipital cortex; vmPFC: ventromedial prefrontal cortex; FPC: frontopolar cortex; Cu/PCu: cuneus/precuneus; MTG/STG/PI/IPC: middle temporal gyrus/superior temporal gyrus/posterior insula/inferior parietal cortex. SPL: superior parietal lobule; PCG: precentral gyrus; mCG/SMA: mid-cingulate gyrus/supplementary motor area; SFG: superior frontal gyrus. Negative Z values represent clusters with higher response to neutral vs. alcohol cues. Voxel P < 0.001, and cluster P < 0.05 FWE corrected. *clusters with a voxel peak meeting P < 0.05, FWE-corrected and the cluster size represents number of voxels meeting this threshold.

reflect participants' awareness of task manipulations, which engaged different regional processes as compared to behavioral scenarios where participants were unaware of the manipulations (Klucken et al., 2009; Tabbert et al., 2010).

Here we showed that, exposure to alcohol as compared to neutral cues elicited regional responses that resemble those reported in earlier cue craving studies (Jasinska et al., 2014). For instance, activities in the visual and medial orbitofrontal cortices may reflect the saliency of alcohol vs. neutral cues. Although not showing increased response to alcohol vs. neutral cues, the thalamus showed higher activation in relation to differences in SCR to alcohol vs. neutral cues. Thus, the thalamus may play a specific role in associating cue exposure to increases in physiological arousal, broadly consistent with altered thalamic functions in drug and alcohol addiction (Huang et al., 2018). A closer examination showed a thalamic cluster concentrated in the intralaminar and mediodorsal nuclei, which are instrumental in regulating arousal and supporting a wide variety of cognitive functions (Hsu et al., 2014; Hsu and Price, 2007; Li and Kirouac, 2008; Van der Werf et al., 2002; Vogt et al., 2008; Wang et al., 2018) > .

The intralaminar thalamus receives dense noradrenergic projections from the locus coeruleus and projects to cortical regions, including the cingulate gyrus, and amygdala to support arousal and responses to salient events (Hsu et al., 2014; Hsu and Price, 2007; Li and Kirouac, 2008; Van der Werf et al., 2002; Vogt et al., 2008). Numerous studies demonstrated that electrical stimulation of the intralaminar thalamus or white matters connecting the intralaminar thalamus altered arousal
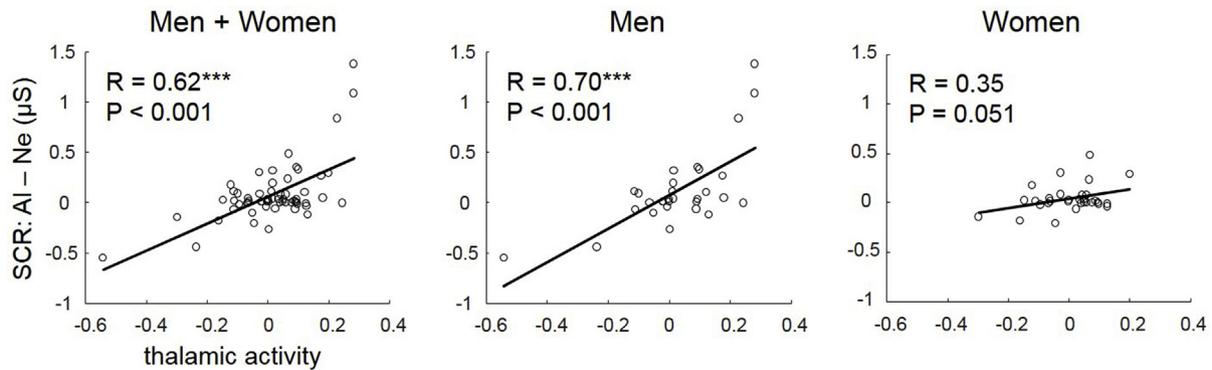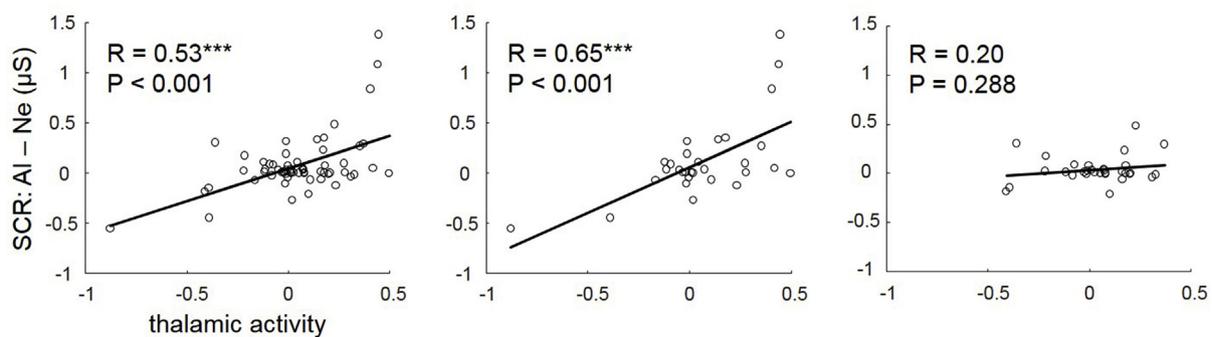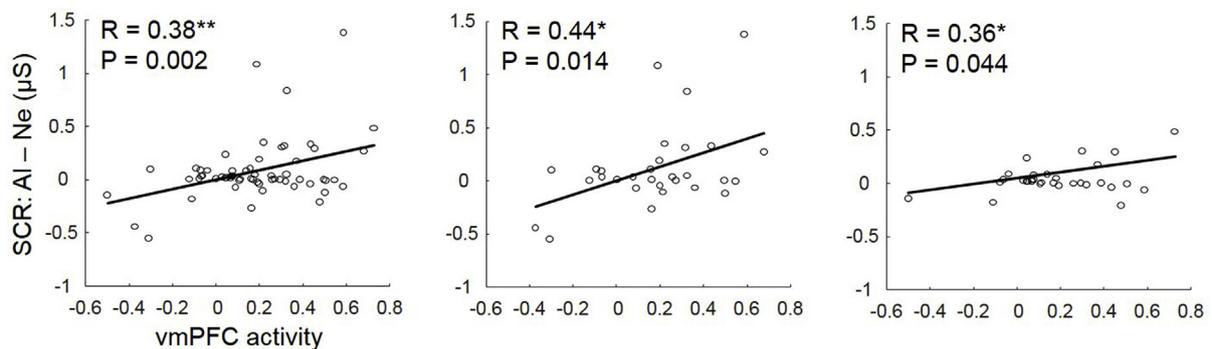
Fig. 3. The correlation between SCR (alcohol – neutral) and thalamic cue response (alcohol – neutral) was significant for the entire sample, as expected. The correlation was also significant for men but not for women. (A) shows linear regressions based on ROI_3 of all three thalamic clusters (bilateral ventroposterior lateral and intralaminar/mediodorsal thalamsus) and (B) shows the regressions based on ROI_1 of the intralaminar/mediodorsal thalamus. (C) shows the regressions of the vmPFC cluster, as identified from region of interest analyses. Both thalamic clusters but not the vmPFC showed significant sex differences in the regression in slope tests (see text for statistics).

and consciousness (Baker et al., 2016; Gummadavelli et al., 2015; Schiff, 2016). It is posited that, by integrating subcortical inputs and cortical responses, the intralaminar nucleus may facilitate synchronization of thalamic cortical activities, gating of attention, and higher level cognitive processes, including memory consolidation (Pereira de Vasconcelos and Cassel, 2015; Saalmann, 2014; Schiff et al., 2013; Varela, 2014). With its dense connections with prefrontal cortical strucutres, the mediodorsal nucleus is known to play a multifaceted role in higher cognitive functions. Alcohol cues elicits craving and cognitive and affective processing in relation to craving, and it remains to be investigated whether the extent of mediodorsal thalamic activation represents an urge to approach or a struggle to avoid alcohol. Together, it appears that, although a number of cortical and subcortical structures

respond more strongly to alcohol as compared to neutral cues, the thalamus plays a unique role in supporting cue-evoked changes in physiological arousal.

4.2. Craving and physiological arousal

Cue reactivity has been a central topic in addiction research. Cue reactivity varies significantly across subjects, and the effect size of cue-evoked physiological responses was relatively small (Carter and Tiffany, 1999), as also shown in the current findings. In cocaine addicted individuals, physiological cue reactivity could not be related to a unitary state of high, withdrawal, or craving (Robbins et al., 1997). A study of methamphetamine-dependent subjects, drug cue-elicited
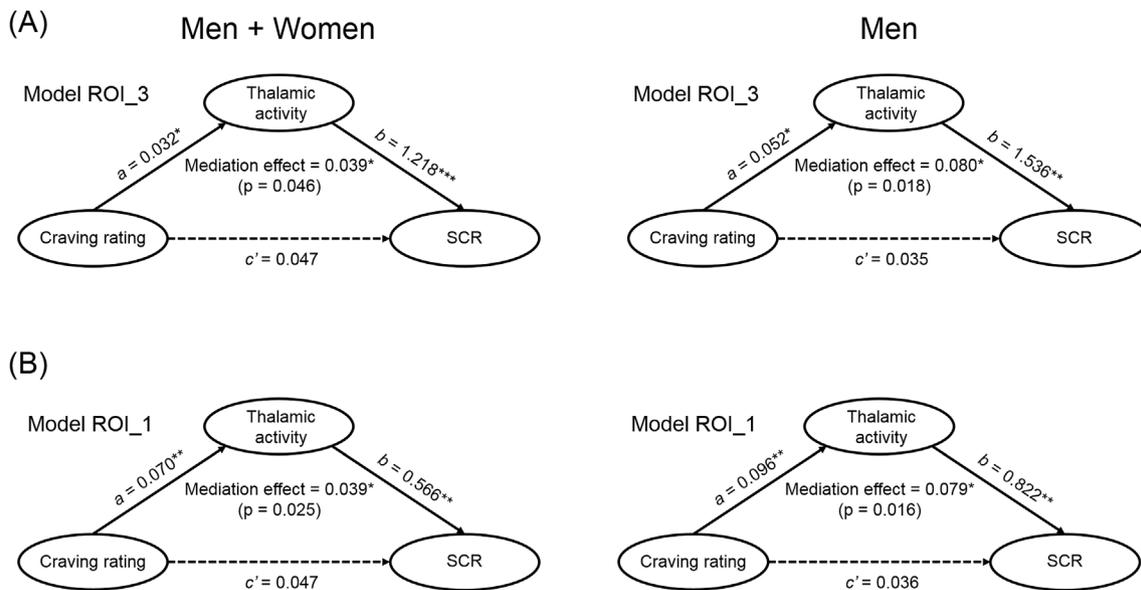
Fig. 4. Mediation analyses showed that thalamic cue activity mediated the correlation between cue-evoked craving and skin conductance response (SCR) in men and women combined (left panels) and in men only (right panels). Thalamic cue activity was computed each of all of the three clusters (ROI_3, A) and the single cluster of the intralaminar/mediodorsal thalamus (ROI_1, B). Mediation analyses were not performed for women as the requirement that X was correlated both with M and Y was not met. The results of mediation for all other models were not significant (Supplementary Tables). The p values of mediation are shown in parentheses. Solid and dotted arrows each represent significant and non-significant correlations. *p < 0.05, **p < 0.01, ***p < 0.001.

craving was not correlated with physiological reactivity, as reflected by heart rate and skin conductance (Tolliver et al., 2010). Here, however, we demonstrated that cue-elicited craving and changes in SCR were correlated in men and women combined as well as in men but not in women alone. These findings suggest that the relationship between craving and physiological reactivity may potentially vary between substances and sexes. Indeed, a review of rodent studies showed that female rats, in general, acquire the self-administration of drugs and alcohol more rapidly, escalate drug taking more rapidly, show more motivational withdrawal and greater reinstatement, with the exception that female rats show less motivational withdrawal from (or "craving for") alcohol (Becker and Koob, 2016).

The literature is limited on the neural processes linking craving and changes in arousal. An earlier study of cannabis users demonstrated higher cue-induced arousal, as indicated by significantly increased skin conductance and a larger late positivity of visual event-related brain potential (Wolfling et al., 2008). However, the physiological and neural reactivity were not correlated. To our knowledge, the current study was the first to query the whole brain for arousal-related regional activations to craving and highlight a specific role of the thalamus in linking craving and physiological manifestations in response to alcohol cues. The findings on the thalamus were broadly consistent with a recent rodent study demonstrating a critical role of thalamic projection to the dorsomedial striatum in the incubation of methamphetamine craving (Li et al., 2018). As discussed above, voxel cue activities peak at the intralaminar and mediodorsal nuclei, in accord with studies supporting these thalamic subregions in the regulation of arousal and other craving-related cognitive and affective processes (Hsu et al., 2014; Hsu and Price, 2007; Li and Kirouac, 2008; Van der Werf et al., 2002; Vogt et al., 2008).

Interestingly, a previous work showed that methylphenidate-induced craving for cocaine in cocaine-dependent subjects was correlated with reduced thalamic dopamine receptor availability (Volkow et al., 1997). A more recent study demonstrated that in alcohol-dependent individuals, citalopram as compared to saline resulted in decreased cue-induced craving for alcohol, and cue-induced alcohol craving was inversely correlated with thalamic but not striatal dopamine D2/3 receptor availability (Zorick et al., 2019). More studies are clearly

warranted to understand the role of physiological arousal and its molecular bases in thalamic responses to craving.

It is worth noting that, although none of the mediation models were significant for the vmPFC, the model that showed the best p values were the same as with the thalamus, and these p values are nearly significant. It is possible that the small sample size may have limited the statistical power to identify a significant mediation.

4.3. Potential sex differences

Compared to men, women showed less craving as elicited by alcohol versus neutral cues. Although no sex differences were noted in the magnitude of SCR, men but not women demonstrated cue-elicited thalamic responses and a positive correlation between cue-elicited craving and SCR. These findings suggest that women may be less vulnerable to cue-induced alcohol craving and thalamic response to physiological arousal during craving, as compared to men, in broad consistency with a large body of literature as discussed earlier. Further, these findings appear to contrast with greater stress-related neural and physiological reactivity in women vs. men as demonstrated across many experimental conditions (Valentino et al., 2012), and suggest the importance of considering sex differences in studying the biological pathways underlying alcohol misuse (Barker and Taylor, 2017).

On the other hand, it is important to note that we did not record or control for menstrual cycling in female participants, who are known to demonstrate differences in electrodermal and neural responses during different menstrual phases (Goldstein et al., 2005; Gray et al., 2009; White and Graham, 2016). More broadly, men and women appeared to show differences in autonomic responses across a wide range of behavioral contexts (Finke et al., 2017; Hubbard et al., 2011; Williams et al., 2005). For instance, physiological reactivity in men but not women was influenced by whether the offers were framed as gain or loss in the Ultimatum Game (Sarlo et al., 2013). Men and women differed in facial electromyographic and autonomic reactions during self-relevance appraisal of gaze direction and dynamic facial expressions (Soussignan et al., 2013). Overall, the findings vary significantly across different experimental manipulations and physiological indices of autonomic responses and defy a simple account of sex differences in terms of

higher or lower responses.

4.4. Limitations of the study and conclusions

A number of limitations need to be considered for the study. First, the study comprised a moderate sample size. Although whole-brain analyses in correlation with SCR demonstrated cue activations confined to the thalamus, we cannot rule out the possibility that a larger sample size may reveal other cortical and subcortical structures to support cue-elicited changes in physiological arousal. Likewise, the SCRs were highly variable, and the current results would need to be confirmed in a larger sample. Second, as discussed earlier, we did not document menstrual cycle in female participants and it is possible that the lack of significant correlations between SCR and regional activities may reflect higher signal variability in women scanned during both follicular and luteal phases. Third, it remains unclear how cue-evoked changes in physiological arousal interact with other psychological constructs, such as impulsivity (Herman et al., 2018; Zhang et al., 2015), in determining alcohol use or how these cross-sectional findings may relate to future drinking behavior. Also, we did not document the time of last alcohol use, which may influence both cue-induced craving and imaging findings. Finally, the neural mechanisms underlying the potential sex differences are not clear. Studies have suggested genetic underpinnings in neural responses to appetitive conditioning (Klucken et al., 2013) and hormonal influences on motivation-related addictive behavior (Becker and Koob, 2016). New experiments and longitudinal follow-ups are required to address these questions.

To conclude, we showed that thalamic cue activity was positively correlated with differences in SCR between alcohol and neutral cue blocks and mediated the correlation between craving and SCR. These findings appear to be carried primarily by male drinkers, who demonstrated higher craving response to alcohol cues than female drinkers. Together, the findings substantiate physiological and neural correlates of alcohol cue response and suggest important sex differences in the physiological and neural processes of cue evoked alcohol craving.

Acknowledgements and disclosures

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.06.005.

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