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ARTICLE

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Sex-specific neural activation to stress and alcohol cues in high-risk drinkers: links between orbitofrontal circuits, alcohol craving, and future drinking

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High-risk drinking is known to disrupt stress and reward pathways including orbitofrontal cortex (OFC) circuits, which may increase cue-induced craving and alcohol use disorder (AUD) risk. Although high-risk drinking is more prevalent in men, it is increasing rapidly among women. It remains unclear whether sex differences in reactivity to stress and alcohol cues contribute to these trends. One hundred eighteen adults (56 high-risk drinkers, 62 low-risk drinkers; 52.5% female) completed an fMRI cue provocation task involving alcohol, stress, and neutral cues in a randomized block design with repeated craving assessments. Linear mixed-effects models tested Group (high-risk, low-risk)-by-Sex-by-Condition (Alcohol, Stress, Neutral) effects on craving and brain activation. High-risk drinkers of both sexes reported greater alcohol cue-induced craving ($p < 0.001$); however, only high-risk women reported increased craving during stress cues ($p = 0.020$). Whole-brain voxel-based analyses ($p < 0.001$, cluster corrected at $\alpha < 0.05$) revealed alcohol cue-related hyperactivation in OFC circuits in high-risk women, but blunted activation in high-risk men. OFC activation correlated positively with craving in women, but negatively in men. During stress cues, high-risk women exhibited increased OFC and hippocampal activation, whereas high-risk men showed heightened amygdala and reduced striatal activity. Decreased stress-related salience network and striatal activity in women but increased activity in men was associated with prospective drinking frequency. These results demonstrate that risky-drinking men and women showed distinct subjective craving and OFC circuit responses to alcohol and stress cues. These sex-specific OFC circuit-related neural patterns may reflect differential risk pathways for AUD and underscore the need for sex-informed prevention and intervention strategies.

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INTRODUCTION

Risky drinking – including binge and heavy alcohol use – is associated with numerous adverse health outcomes and constitutes a major public health issue [1, 2]. Beyond acute problems such as hangovers, blackouts, and accidents [3, 4], risky drinking significantly increases the risk for developing alcohol use disorder (AUD) [5, 6] and all-cause mortality [7]. Despite its prevalence, the mechanisms driving the escalation from moderate to risky levels of drinking remain poorly understood.

One potential mechanism underlying risky drinking is heightened reactivity to stressors and alcohol-related cues, which are common triggers for craving and relapse in individuals with AUD [8]. These stimuli activate the orbitofrontal cortex (OFC) and its associated circuitry [9]. The OFC has both structural and functional connections to the striatum, limbic regions (hippocampus, amygdala, hypothalamus, thalamus), and salience network regions (anterior cingulate cortex [ACC], anterior insula) [10, 11]. Further, it can be divided into lateral and medial subregions with dissociable functions. In general, the medial OFC is implicated in reward learning and hedonic processing, while the lateral OFC is involved in processing of aversive stimuli and has greater functional connectivity with cognitive control and executive networks [10]. Both subregions have been associated with dysfunction in self-control and decision-making related to problematic alcohol use [10, 12, 13]. For example, dysfunction in OFC-related circuitry has been associated with higher craving [12, 14, 15], problematic drinking behavior [16–18], and AUD diagnosis [12, 15, 19], and may reflect both vulnerability to and consequences of alcohol misuse [20]. Greater reward-related striatal and OFC activation during adolescence may predict future heavy drinking [18, 21, 22], while chronic heavy drinking has been linked to blunted VmPFC/OFC-striatal responses to alcohol cues [17, 23–25], potentially reinforcing continued heavy use. To clarify the role of this circuitry in the development of harmful drinking, it is essential to examine neural cue reactivity across the spectrum of drinking behavior. While OFC-striatal-limbic responses to stress and alcohol cues have been documented in healthy individuals [9] and those with AUD [17, 19], little is known about how this circuitry functions in risky drinkers without AUD despite other evidence of neural differences in this population (e.g.,[26–30]).

Sex differences may further shape the neural and behavioral mechanisms underlying risky drinking. Although men have

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historically reported higher rates of alcohol consumption, risky drinking, and AUD, recent epidemiological studies show a dramatic increase in alcohol use in women, narrowing the gender gap [31–33]. The fact that the prevalence of risky drinking is changing at different rates for men and women suggests the possibility of different mechanisms for problematic alcohol use. However, women have historically been underrepresented in mechanistic studies of alcohol problems [19, 34], despite growing evidence of meaningful sex differences [35–38]. For example, stress exposure, negative affect, and related psychopathology (e.g., depression, PTSD) are often more strongly linked to alcohol outcomes in women [39–41]. In fact, women are far more likely to develop a new onset AUD or experience a relapse following stressful life events, a finding that is mirrored in preclinical data using rodent models [39]. Nevertheless, relatively few studies have explored whether neural responses to stress and alcohol cues may help explain distinct risk pathways for men and women [42].

To address this gap, the present longitudinal observational study used functional magnetic resonance imaging (fMRI) to investigate sex-specific neural responses to stress and alcohol cues, and their associations with craving and future drinking, in a large sample of nondependent but risky male and female drinkers. Participants completed a well-validated fMRI paradigm [43, 44] involving stress, alcohol, and neutral-relaxing cues, rated their craving during the task, and reported their daily alcohol consumption for 30 days following the scan. Based on prior findings in AUD samples [16, 37, 42], we hypothesized that high- relative to low-risk drinkers would show dysregulated OFC and related circuit responses to stress and alcohol cues, with distinct patterns between men and women. We also hypothesized that sex-specific differences in brain activation between high- and low-risk drinkers would be associated with alcohol craving and future drinking behavior, suggesting distinct etiological pathways of risky drinking for men and women.

MATERIALS AND METHODS

Participants and Procedure

Participants ($N = 118$) were recruited from the greater New Haven, Connecticut area via internet advertisements and posted flyers. Study procedures were approved by the Yale University Institutional Review Board. All participants provided written informed consent after receiving a complete description of the study and prior to commencing study procedures.

At intake, participants reported their demographic information including race and biological sex. Participants completed assessments to determine drinking risk status (high vs low), including the Cahalan Quantity Frequency Variability Index to assess past-month [45] and the Alcohol Use Disorders Identification Test (AUDIT[46]) to assess past-year alcohol use. Based on NIAAA criteria for binge and heavy drinking [47], participants were categorized as low-risk ($N = 62$, 54.8% female) or high-risk drinkers ($N = 56$, 50% female). High-risk drinkers reported engaging in binge drinking (defined as ≥ 4 drinks for women, ≥ 5 for men per occasion) on four or more occasions per year and/or weekly consumption of ≥ 8 drinks (women) or ≥ 15 drinks (men), without meeting criteria for current moderate or severe AUD. Low-risk drinkers did not meet these criteria and had no AUD history (see Supplemental Materials for more detail).

Following intake assessments, participants underwent fMRI while completing a well-validated cue provocation task. A subset of participants ($N = 96$, 81%) also participated in a phase two prospective data collection that involved daily alcohol use self-reports via a smartphone app (Metricwire, Inc) for 30 days post-scan.

fMRI Methods and Procedures

Cue-provocation paradigm. During fMRI, participants completed a well-validated cue provocation task [16, 17, 44] featuring three randomized blocks of alcohol-related, stress-inducing, and neutral/relaxing control visual images. Images were selected from the International Affective Picture System IAPS [48] or developed and validated by the Yale Stress Center as previously outlined [17, 44, 49]. Alcohol images included pictures of a range of alcoholic beverages (e.g., wine, mixed drinks, beer) on their own or being consumed, stressful images contained themes of violence, danger (e.g., a venomous snake), or disgust (e.g., a sink overflowing with dirty dishes), and neutral/relaxing images included nature and other peaceful scenes.

Each condition block (alcohol, stress, neutral) contained three one-minute baseline runs (gray fixation period) followed by six one-minute imagery runs (provocation). Each provocation run involved presentation of 11 condition-specific visual images for 5 seconds with a 1 s interstimulus interval. After each run, participants rated their subjective levels of alcohol craving and stress on a 9-point Likert scale (see Supplement for details).

fMRI acquisition. Scanning was conducted on a 3 T multiband Siemens Trio or Prisma MRI system using a standard quadrature head coil. High-resolution structural images were acquired using a T_1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence. Functional images were obtained using T_2^* -sensitive, gradient-recalled, single-shot echo-planar imaging (EPI) pulse sequences.

Data Analytic Approach

Demographic and behavioral analyses. Group (high- versus low-risk) and sex differences in demographic and clinical variables were examined using one-way ANOVA and Pearson chi-square tests. Linear mixed-effects models with a random intercept varying by participant were estimated to evaluate group-by-sex-by-condition (alcohol, stress, neutral) interaction effects on subjective in-scanner alcohol craving and stress ratings, adjusting for age and run order (runs 1–6). Craving and stress ratings during each of the provocation runs were baseline-corrected by subtracting the average rating from the corresponding condition's three baseline (gray fixation) runs. All statistical tests were two-tailed and were statistically significant at $\alpha = 0.05$. Analyses were conducted and graphed using R [50].

fMRI preprocessing and group level analyses. fMRI data were preprocessed and analyzed using a combination of tools (as detailed in the Supplement Materials). First-level general linear model (GLM) analyses modeled each provocation run relative to the corresponding baseline (gray fixation) period, generating condition-specific contrast maps (provocation minus baseline). The resulting contrast maps were entered into second-level whole-brain voxel-wise analyses using AFNI (version 23.1.07).

To examine whether neural activation for the alcohol, stress, and neutral contrasts differed between high- and low-risk drinkers–and whether any group differences varied by sex–we estimated a linear-mixed effects model using AFNI's 3dLME (version 2.0.9). The model examined main and interactive effects for condition (alcohol, stress, or neutral image relative to baseline for each run) as a within-subject fixed-effect, group (low-risk vs. high-risk) and sex (male vs. female) as between-subjects fixed-effects, with a random intercept varying by participant. Age and task run were included as covariates of no interest. The neutral condition served as an active control to account for nonspecific task-related effects. Accordingly, alcohol minus neutral and stress minus neutral contrasts were computed during post-hoc testing; results from these contrasts are reported along with the neutral condition alone.

Next, to explore associations between neural responses in each condition and subjective craving during fMRI, and sex differences, we conducted linear mixed-effects regression analysis testing condition-by-craving and condition-by-craving-by-sex interactions. To further explore whether task-related activations were related to future drinking behavior within or across sexes, we estimated an additional linear mixed-effects regression assessing condition-by-drinking frequency (i.e., percentage of drinking days over 30 days) and condition-by-drinking frequency-by-sex interactions. We chose to examine associations with future drinking behavior rather than past drinking as these data were reported daily after the fMRI scan and therefore less subject to recall bias. These linear mixed-effects regression models were limited to high-risk drinkers due to low craving and drinking frequency observed in the low-risk group.

For all whole-brain analyses, family-wise error (FWE) correction was applied based on Monte Carlo simulations conducted with AFNI's 3dClustSim (version 22.6.24). Spatial autocorrelation estimates were obtained using 3dFWHMx on the residuals from the 3dLME models and then used as input into 3dClustSim. Clustered activations were considered statistically significant if they survived whole-brain FWE correction at $\alpha = 0.05$, using a voxel-wise threshold of $p < 0.001$.

Table 1. Clinical and demographic variables by drinking group and sex.

Characteristic	Low-risk Drinkers $N = 62$				High-risk Drinkers $N = 56$			
	Male ($N = 28$)		Female ($N = 34$)		Male ($N = 28$)		Female ($N = 28$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	30.67	10.50	30.76	9.84	26.64	7.96	27.00	9.33
Education (years)	16.15	2.12	15.88	2.53	15.47	1.84	15.20	2.14
Shipley IQ Estimate	113.04	8.28	113.58	6.50	114.96	5.17	115.32	6.25
Baseline Average drinks per drinking day	2.04	1.16	1.38	0.70	4.5	2.15	3.50	1.53
Baseline Percentage of drinking days	17.49	18.40	14.97	14.53	40.67	21.98	31.68	19.25
AUDIT	3.20	2.42	2.52	1.33	8.93	3.98	7.61	3.47
Depression symptoms	4.89	6.42	5.68	6.42	5.36	6.93	6.39	5.31
	N	%	*N*	%	*N*	%	*N*	%
Race								
White	14	50.0	21	61.76	18	64.29	19	67.86
Black	5	17.86	7	20.0	5	17.86	6	21.43
Asian	3	10.71	5	14.71	0	0	2	7.14
Other	6	21.43	1	2.94	5	17.86	1	3.57
DSM-5 Diagnoses:								
Current mood disorder	3	10.7	5	14.7	1	3.6	1	3.6
Current anxiety disorder	1	3.6	10	29.4	1	3.6	3	10.7
Current non-alcohol SUD[a]	0	0	0	0	1	3.6	2	7.1
Lifetime mood disorder[b]	5	17.9	11	32.4	3	10.7	7	25.0
Lifetime anxiety disorder[b]	1	3.6	12	35.3	1	3.6	5	17.9
Lifetime SUD	1	3.6	0	0	6	21.4	4	14.3
Current smoker	2	7.14	0	0	3	10.71	4	14.29
Current cannabis user[c]	2	7.14	3	8.82	9	32.14	10	35.71
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Prospective Drinking:								
Average drinks per drinking day	1.86	1.81	1.49	1.22	5.86	3.40	3.60	1.12
Percentage of drinking days	19.12	24.58	13.96	16.28	46.32	27.48	38.53	20.96
Percentage of heavy drinking days	3.92	9.13	2.04	3.51	20.90	17.15	15.90	11.28

[a] The only current non-alcohol SUD in this sample was cannabis use disorder.
[b] Includes obsessive-compulsive and trauma related disorders.
[c] Defined as participants who endorsed using cannabis at least once in the past month.
Drinking groups (male high-risk, female high-risk, male low-risk, female low-risk) were matched on baseline demographic and clinical characteristics (i.e., no significant group differences were found; *p*-values > 0.05, two-sided) except that low-risk women had higher rates of current ($X^2(3) = 10.40$, $p = 0.015$) and lifetime ($X^2(3) = 13.0^2$, $p = 0.004$) anxiety disorders (including obsessive-compulsive and trauma-related disorders) compared to other groups and there were more current marijuana users in the high-risk women group ($X^2(3) = 11.79$, $p = .008$). High-risk men and women had higher baseline average drinks ($F(3,113) = 28.16$, $p < 0.001$), percent drinking days ($F(3,113) = 12.62$, $p < 0.001$) and AUDIT scores ($F(3,106) = 31.61$, $p < 0.001$) than low-risk groups, but there were no significant sex differences within groups. Baseline alcohol use measures reflect last month drinking while prospective drinking variables reflect the 30 days following the scan. Depression symptoms were measured using the Beck Depression Inventory. See supplemental table S1 for demographic information on the subset who reported prospective drinking. *SUD* substance use disorder, *AUDIT* Alcohol Use Disorders Identification Test.

RESULTS

Baseline demographic and clinical characteristics

There were no significant group and sex differences in age, education, IQ, race, smoking status, mood and non-alcohol substance use disorders. However, low-risk women had higher rates of current and lifetime anxiety disorders than other groups. High-risk drinkers reported greater baseline average drinks per drinking day, percent drinking days, higher AUDIT scores, and past-month cannabis use than low-risk drinkers, with no sex differences within risk groups (see Table 1).

Group and sex differences in behavioral responses during fMRI

We observed a main effect of condition on cue-induced craving ($F(2, 1985) = 239.72$, $p < 0.001$) qualified by a significant group-by-sex-by-condition interaction ($F(2, 1985) = 9.55$, $p < 0.001$). Across all participants, craving was higher during alcohol relative to both stress ($b = 0.52$, $p < 0.001$) and neutral ($b = 0.75$, $p < 0.001$) conditions, and higher in the stress than neutral condition ($b = -0.23$, $p < 0.001$). Post-hoc tests showed that high-risk men reported significantly greater craving than low-risk men only during alcohol cues ($b = -0.54$, $p < 0.001$), whereas high-risk women reported elevated craving to both alcohol ($b = -0.49$, $p < 0.001$) and stress cues ($b = -0.29$, $p = 0.02$) relative to low-risk women (Fig. 1). Group and sex differences in stress ratings are detailed in the Supplement (Figure S2).

Group and sex differences in neural activation to stress and alcohol cues

Whole-brain voxel-wise 3dLME analyses yielded significant main effects of condition, and condition-by-group and condition-by-group-by-sex interactions (for condition main effects see Table S2).

Simple effects of the condition-by-group interaction showed that, relative to the low-risk group, the high-risk group exhibited greater left putamen activation in the alcohol-neutral contrast. In the stress-neutral contrast, the high-risk group showed hyperactivation in the posterior cingulate cortex (PCC) and parts of the salience network (dorsal ACC, posterior left insula) but hypoactivation in the rostral anterior cingulate (rACC) (Fig. 2, Table S2).

We also observed a condition-by-group-by-sex interaction (Fig. 3, Table S3). Compared to low-risk men, high-risk men showed hypoactivation in the left OFC as well as the hypothalamus, left hippocampus, striatum (caudate, nucleus accumbens [NAcc]), bed nucleus of the stria terminalis (BNST), and the right anterior insula during alcohol relative to neutral cues. During stress-neutral cues, high-risk men again showed blunted NAcc and BNST responses but hyperactivation in the ventrolateral prefrontal cortex (vlPFC), left amygdala, and right hippocampus. During the neutral control condition, high-risk men had relatively hyperactive responses in the striatum, BNST, and right anterior insula.

Group differences between high- and low-risk drinkers manifested differently in women (Fig. 3, Table S2). While high-risk men exhibited blunted activation to alcohol cues compared to sex-matched low-risk controls, high-risk women showed heightened activation in the OFC and associated limbic regions (ventral hypothalamus, bilateral hippocampus), but reduced activation in the right vlPFC. In the stress-neutral contrast, high-risk women displayed hyperactivation in the OFC and right hippocampus, and hypoactivation in the left anterior insula. No group differences among women emerged during the neutral condition.

Fig. 1 Self-reported alcohol craving by condition (Alcohol, Stress, Neutral), drinking group (high-risk vs low-risk), and sex. Craving during baseline runs (gray fixation) was subtracted from craving during provocation (imagery) runs to yield cue-provoked craving ratings. High-risk drinkers reported significantly greater craving to alcohol cues than sex-matched low-risk controls. High-risk women also reported greater craving to stress cues than low-risk women. *indicates a statistically significant group difference within sex for that condition ($p < 0.05$). Error bars represent the standard error of the mean (SEM).

Neural correlates of provoked craving and sex differences. Whole-brain voxel-wise 3dLME analyses revealed significant condition-by-craving and condition-by-craving-by-sex interactions in cortico-limbic-striatal activation among high-risk drinkers (Fig. 4A; Table S3). Across all high-risk drinkers, greater craving was associated with increased putamen activation during neutral cues, but blunted activation during alcohol- and stress-neutral contrasts. In women, greater craving was associated with blunted left OFC activation to neutral cues and increased activation to alcohol-neutral and stress-neutral cues; men showed the opposite pattern but in the right OFC. A similar sex-specific dissociation emerged in the insula during the stress-neutral contrast: greater

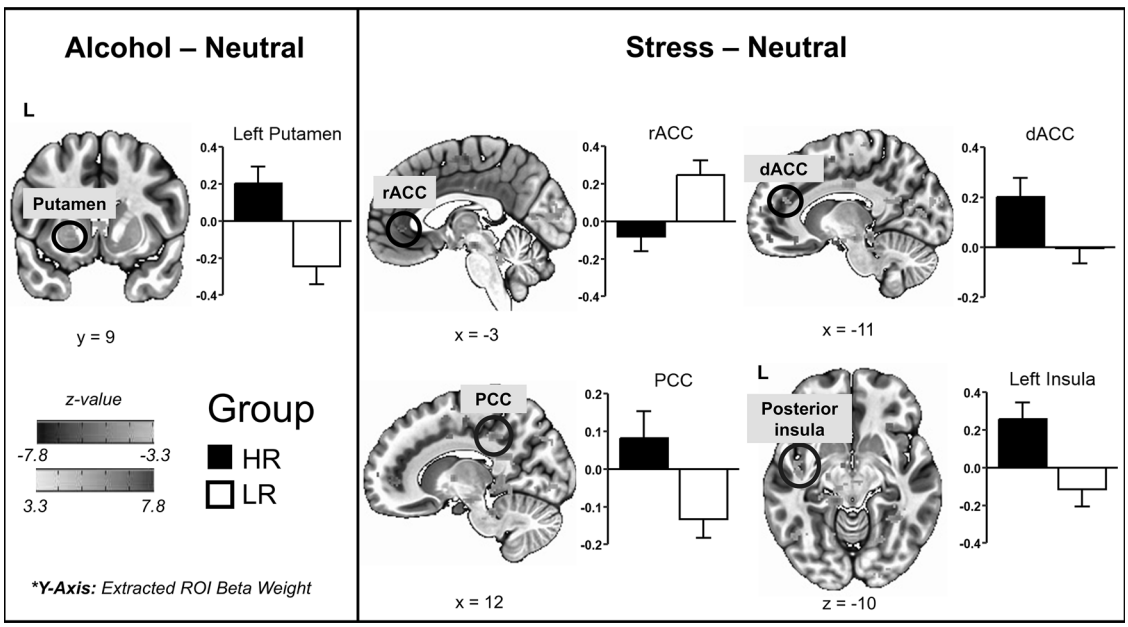


Fig. 2 Whole-brain voxel-wise linear mixed-effects analyses assessed condition-by-group interactions in cortico-striatal-limbic regions. Brain slices depict significant ($p < 0.001$, cluster corrected at $\alpha < 0.05$) post-hoc differences in activation during the alcohol and stress conditions relative to neutral between the high-risk and low-risk groups with yellow to red colors indicating relative hyperactivation and blue indicating relative hypoactivation in high-risk versus low-risk drinkers. Analyses adjusted for age and scan run. Bar plots show the average change in region-of-interest (ROI) beta weights for the high-risk and low-risk groups. Error bars represent the standard error of the mean (SEM). rACC rostral anterior cingulate cortex, dACC dorsal anterior cingulate cortex, PCC posterior cingulate cortex, HR High-risk drinkers, LR low-risk drinkers.

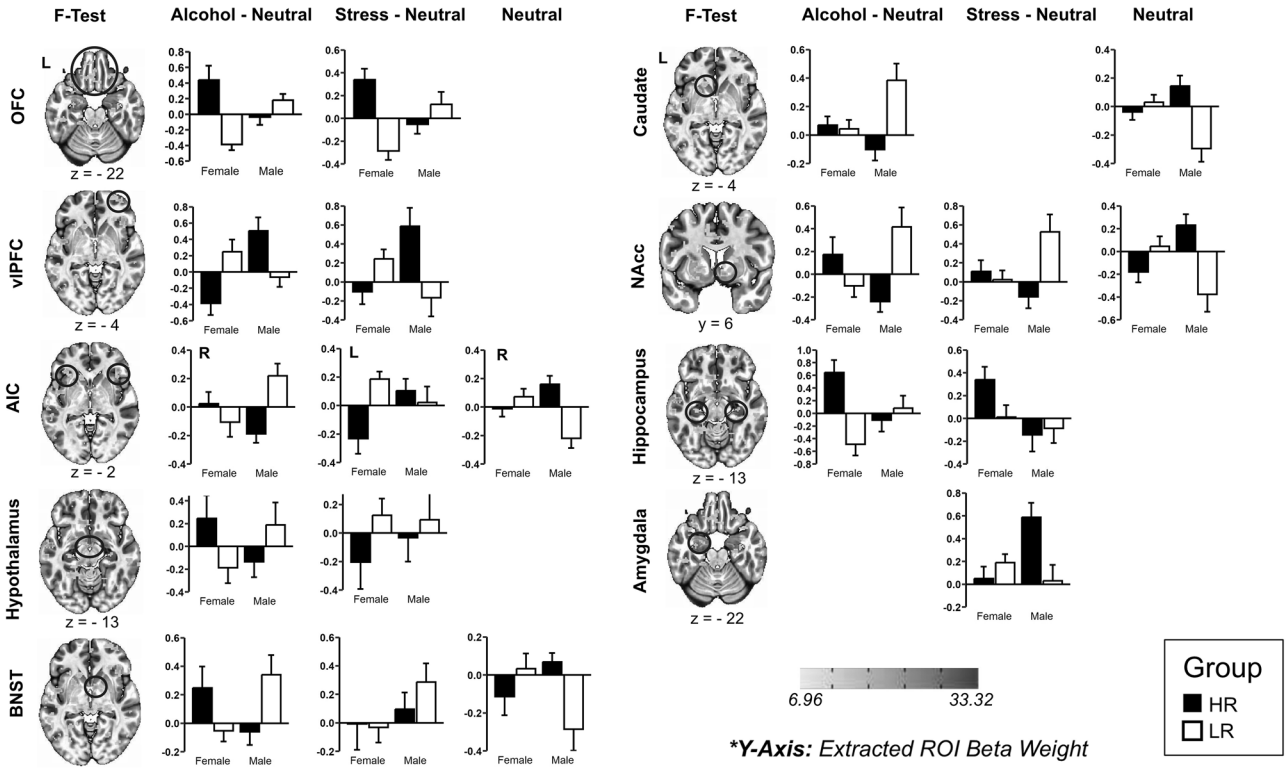


Fig. 3 Whole-brain voxel-wise linear mixed-effects analyses adjusting for age and scan run depict significant condition-by-group-by-sex interactions in cortico-striatal-limbic activation. Yellow to red heatmap colors on brain slices reflect the significance of the F-test of the three-way interaction ($p < 0.001$, cluster corrected at $\alpha < 0.05$) but do not indicate the direction of the effect. Bar plots show the average change in region-of-interest (ROI) beta weights for the high-risk and low-risk groups by sex. More positive beta weights indicate greater hyperactivation in a given ROI while more negative beta weights indicate greater hypoactivation. Error bars represent the standard error of the mean (SEM). AIC Anterior insular cortex, BNST bed nucleus of the stria terminalis, NAcc nucleus accumbens, OFC orbitofrontal cortex, vlPFC ventrolateral prefrontal cortex, HR high-risk drinkers, LR low-risk drinkers.

craving correlated with increased insular activation in women, but decreased activation in men. Additionally, increased vlPFC activation during the stress-neutral contrast was positively associated with craving in women only.

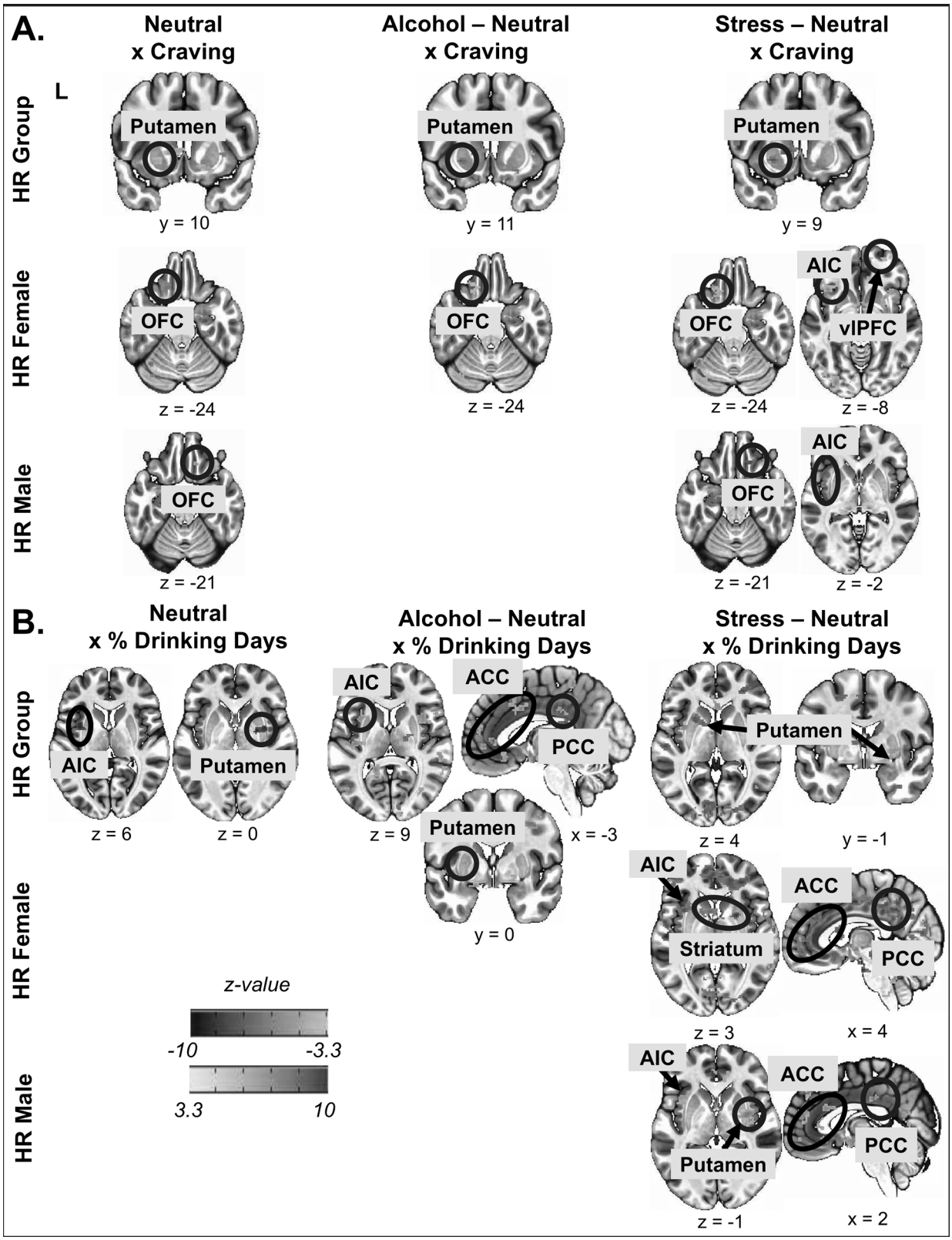
Neural correlates of prospective drinking and sex differences. In high-risk drinkers, whole-brain voxel-wise linear mixed-effects regression analysis revealed condition-by-drinking frequency and condition-by-drinking frequency-by-sex interactions in cortico-limbic-striatal regions (Fig. 4B; Table S4). Among all high-risk drinkers, hypoactivation in the left insula and right putamen to neutral cues was associated with more frequent drinking. In the alcohol-neutral contrast, hyperactivation of the salience network (rACC, dACC, left insula), the PCC, and left putamen were associated with more frequent future drinking. A sex-specific pattern emerged in these regions in the stress-neutral contrast: in men, hyperactivation of these regions was linked to more frequent drinking, whereas in women, hypoactivation was associated with increased drinking frequency.

DISCUSSION

The present study examined whether high-risk male and female drinkers show distinct patterns of OFC and related circuit activation to stress and alcohol cues relative to sex-matched controls, and whether any differences were associated with concurrent craving and prospective drinking behavior. We found that high-risk drinkers, relative to their low-risk counterparts, showed specific differences in cue-related neural activity, such as increased left putamen activity to alcohol cues, that related to craving and future drinking. However, the OFC and related cortico-limbic-striatal circuitry showed sex-specific differences in activation to stress and alcohol cues, which were also associated with concurrent craving and future drinking frequency. While prior studies have reported sex-specific differences in neural responses to alcohol and stress cues in social drinkers [9] and individuals with AUD [16, 42], this is the first study to our knowledge reporting findings on sex differences in OFC and related circuit responses to stress and alcohol cues among risky-drinking men and women. This is an important demographic as it constitutes a much larger percentage of the population than those with AUD [51] and carries numerous health risks [3, 4, 7] including greater likelihood of future AUD [5, 6]. The current findings extend the literature by showing that alcohol-related neural activation manifests in a sex-specific manner with important implications for understanding and addressing harmful alcohol intake and AUD risk. Critically, such differences suggest the presence of sex-specific neurobiological mechanisms underlying high-risk drinking, potentially mediated by differential associations with craving [8] and drinking behavior.

As expected, the cue-provocation task elicited significantly greater subjective craving in the alcohol and stress conditions compared to the neutral condition across all participants, with high-risk drinkers reporting greater craving than low-risk drinkers during alcohol cues. However, only high-risk women and not men reported increased craving during the stress condition. This corroborates evidence that women are more likely to drink to alleviate stress and negative affect [39, 40] and further supports the idea that mechanisms underlying harmful drinking may vary by sex.

Neural reactivity to alcohol and stress cues also differed by sex, notably with the OFC emerging as a key region for these differences. The OFC is involved in reward processing and decision



making [13, 52] and is part of a circuit that is common to both craving and stress [10, 12, 13, 53]. However, some inconsistencies in the directionality of prior associations between craving and stress and this circuitry may be due to sex differences [12]. The present results support this possibility. For one, the medial OFC was hyperactive to stress and alcohol cues in high- relative to low-risk women. Further, among high-risk women, greater left lateral OFC activation to these cues was associated with greater subjective alcohol craving. In men, however, medial OFC was hypoactive to alcohol cues in high-risk drinkers and OFC

Fig. 4 Whole-brain voxel-wise linear mixed-effects regression analyses assessed neural correlates of in-scanner craving and prospective drinking frequency in high-risk drinkers. Whole-brain voxel-wise post hoc linear mixed-effects regression analysis ($p < 0.001$, cluster corrected at $\alpha < 0.05$) adjusting for age and task run shows that craving was associated with shared and sex-specific disruptions in cortico-limbic-striatal activation patterns in response to neutral images and alcohol and stress images relative to neutral in high-risk drinkers (**A**). Whole-brain voxel-wise post hoc linear mixed-effects regression analysis ($p < 0.001$, cluster corrected at $\alpha < 0.05$) adjusting for age and task run shows that prospective 30-day drinking frequency (percentage of drinking days out of 30-day follow-up period) was associated with shared disruptions in cortico-limbic-striatal activation patterns in response to neutral images and alcohol and stress images relative to neutral images in high-risk drinkers. Sex-specific activation patterns emerged in response to stress relative to neutral images (**B**). Yellow to red colors indicate positive associations while blue indicates negative associations. OFC orbitofrontal cortex, vlPFC ventrolateral prefrontal cortex, AIC anterior insular cortex, ACC anterior cingulate cortex, PCC posterior cingulate cortex, HR high-risk drinkers.

hypoactivation to stress cues was linked with greater alcohol craving. Together, these results suggest that over-recruitment of the OFC in response to stressors or alcohol cues may serve as a marker of risky drinking specifically for women while under-recruitment may be a risk marker in men.

Another notable sex difference in neural activation was that high-risk men but not women showed striatal and insular hyperactivation to neutral cues compared to their low-risk counterparts. This finding is consistent with prior work showing that greater baseline activation of reward circuitry is a particular feature of AUD risk for men [21]. Perhaps because of this greater baseline activation, high-risk men showed largely hypoactivated cortico-striatal-limbic circuitry to alcohol cues, whereas high-risk women showed the opposite pattern with heightened activation in the OFC, hypothalamus, and hippocampus. Prior studies have found the reverse pattern in AUD with greater alcohol-cue-related hyperactivation of cortico-limbic-striatal circuitry in men versus women [16, 36, 37] (though see [54]), but no differences in these regions in social drinkers [9]. This suggests that sex differences in OFC-related limbic-striatal activation to alcohol cues may emerge in high-risk drinkers and then reverse direction with escalating alcohol use and tolerance, though longitudinal studies are needed to explore this possibility.

Understanding which sex differences in alcohol- and stress-related neural reactivity are linked to prospective drinking behavior is essential to understanding the maintenance of risky drinking behavior. Much of the circuitry associated with future drinking frequency was shared across male and female high-risk drinkers, with greater cortico-striatal-limbic activation to alcohol cues linked with more frequent drinking [18, 55]. The only condition-by-drinking frequency-by-sex interactions emerged in the stress condition, with a widespread pattern of hypoactivation across the striatum and salience network related to more frequent drinking in women but hyperactivation in those regions related to more frequent drinking in men. These results imply that heightened or blunted activation of the salience network and striatum during stress may be a source of vulnerability depending on a person's sex. Though few prior studies have specifically assessed how neural reactivity to stressors is related to future drinking behavior, dysregulation of the HPA axis has been linked to future risky drinking [56, 57]. Women typically show less cortisol or physiological reactivity but greater distress in response to stress challenges [56]. This under-recruitment of the stress response may increase the likelihood that women use substances to self-regulate.

In addition to meaningful sex differences in the OFC and related circuit response to alcohol and stress cues, high-risk drinkers of both sexes showed greater putamen activation in response to alcohol cues. This heightened activation likely reflects neural adaptations resulting from heavy alcohol intake, as the putamen is known to be implicated in habit formation, craving, and compulsive drug seeking, and shows elevated response to alcohol cues in individuals with AUD [16, 55, 58, 59]. Interestingly, although high-risk drinkers showed increased putamen activation to alcohol cues compared with low-risk drinkers, alcohol cue-related putamen activity was inversely related to craving within that group. In contrast, greater putamen activation to alcohol cues was positively associated with future drinking frequency. This pattern suggests that subjective craving and future alcohol use may be driven by distinct striatal processes. While higher putamen response may reflect heightened cue-reactivity that facilitates future drinking, risky-drinking individuals reporting greater craving may show reduced striatal engagement, potentially reflecting compensatory neuroadaptation or motivational dysregulation. Similar associations between the putamen, craving, and drinking behavior have been observed in a sample of AUD participants [16], highlighting the importance of this region as one that is both dysregulated by heavy alcohol use and predictive of future alcohol consumption [60] regardless of sex.

The present study has several strengths and addresses limitations of previous studies. Very few studies have examined neural responses to both alcohol and stress cues in high-risk drinkers [61], a crucial stage for understanding the impacts of heavy or binge alcohol use and vulnerability to alcohol addiction, and no prior study examined sex differences. The robust sample with whole-brain voxel-based analyses of the present study allowed for a thorough investigation into sex differences in alcohol- and stress-related neural mechanisms of craving and drinking behavior, thereby informing sex-specific pathways of risk and providing insights for future preventative interventions. However, there are also noteworthy limitations. For one, this is a cross-sectional investigation of neural responses to stress and alcohol cues. Therefore, we cannot dissociate pre-existing risk factors for heavy drinking from its consequences. Given that participants did not receive any intervention targeting their drinking, we can assume that the neural correlates of future drinking would also relate to past drinking history. Longitudinal brain imaging studies are needed to untangle consequences of risky drinking from risk markers for escalation of drinking problems. Lastly, craving ratings during the scan were modest. Nonetheless, meaningful associations emerged between craving and neural activation in high-risk participants, suggesting that these relationships may be robust even at subclinical levels. Future research should examine whether similar brain-craving associations emerge in high-risk drinkers with higher levels of craving.

In conclusion, the present study is the first to demonstrate that non-dependent, risky-drinking men and women exhibited both shared and distinct patterns of neural reactivity to stress and alcohol-related cues. While some of these patterns of neural responses resembled those observed in individuals with AUD–such as increased putamen activation to alcohol cues–other patterns specifically pertaining to OFC and related regions were unique, potentially reflecting a distinct neural phenotype associated with heavy alcohol consumption when symptoms such as impaired control, tolerance, and alcohol-related problems that characterize AUD are still absent. Evidence of sex differences in cue-provoked craving and activation of OFC and related circuits that were associated with craving and future drinking indicates that sex is an important variable to consider in understanding the mechanisms of risky drinking and pathways to AUD. Future research should continue to examine whether these sex-specific patterns can inform the development of tailored prevention and early interventions.

DATA AVAILABILITY

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

RS and DS acquired funding for the project. RS conceptualized the study. RS and MR designed the analysis plan. CL processed the neuroimaging data. CF and MR analyzed the data. CF, MR, and RS interpreted the findings. CF wrote the initial draft of the manuscript and MR, JM, DS, and RS provided critical revisions. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

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