



Sex Differences in Neural Responses to Stress and Alcohol Cues Among Risky Social Drinkers

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BACKGROUND

High-risk drinking is associated with adverse health consequences^{1,2} including increased risk for alcohol use disorder or AUD.³

Recent studies indicate sex-specific drinking motivation and drinking behaviors^{1,2} as well as neural responses to stress and alcohol cues^{6,7,8}

e.g., Men tend to drink more in general, while women who develop AUD are more likely to display a more addictive form of illness.^{4,5}

Yet, little is known about the sex-specific neural mechanisms underlying high-risk drinking. Identification of these mechanisms is a critical step to better understand sex-specific mechanisms of AUD risk and developing appropriate prevention and treatment strategies.

The Current Study

The current study investigated sex differences in neural responses to stress and alcohol cues, as well as in neural correlates of alcohol craving, and their associations with drinking behavior in high-risk drinkers, but without alcohol dependence using functional magnetic resonance imaging (fMRI).

METHOD

Participants were 94 social drinkers (mean age = 29.18; 42 females) - demographically-matched heavy or binge (HB) (n=49) and light-moderate (LM) drinkers (n=45)

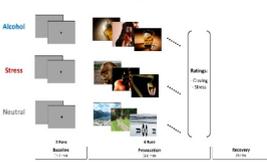
Table 1. Basic Demographics and Background Information.

	Men	Women	Overall	Men	Women
	n=52	n=42	N=94	LM drinkers n=25	HB drinkers n=22
Demographics					
Age (in years)	28.8(9.53)	29.6(9.69)	29.2(9.50)	31.8 (10.70)	30.2(9.81)
Education (in years)	15.8(1.89)	15.8(2.51)	15.8(2.19)	16.3(1.99)	15.4(1.72)
Shapley (IQ)	115(6.00)	114(6.98)	114.6(6.45)	114(7.05)	118(4.78)
Race (% Caucasian)	60%	62%	61%	27%	33%
Baseline drinking					
Max drinks	6.4(3(4.7)	4.9(2.32)	5.7(3.08)	4.1(2.14)	8.4(9(4.49)
AUDIT total score	6.2(2(4.40)	5.1(2(3.65)	5.7(4.00)	3.2(2(2.50)	8.9(6(4.90)
Years of alcohol use	5.8(9(7.40)	6.6(2(5.95)	6.2(1(6.78)	5.8(3(6.41)	5.4(9(5.10)

No significant differences were observed in demographics or baseline drinking between men and women or in demographics between HB and LM drinkers within each gender (all ps>0.05).

During an fMRI session, a well-validated emotion provocation task⁹ was administered, where participants viewed stress, alcohol, and neutral cues and rated their alcohol craving and stress.

fMRI paradigm



3T Prisma MRI scanner

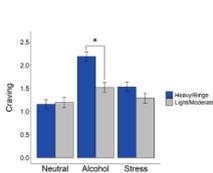


fMRI paradigm—Emotion Provocation task:

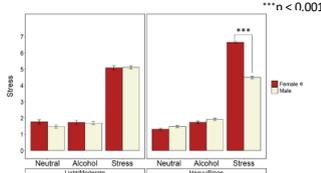
- 3 blocks: stress, alcohol-cue, and neutral-relaxing cues
- Each block: 3 baseline runs (grey blanks) + 6 provocation runs (stress, alcohol, or neutral pictures)
- Each run: 11 images + alcohol craving and stress ratings
- After completing the 6 provocation runs, rest for 4 minutes during the recovery phase (no images)

RESULTS

Alcohol Craving

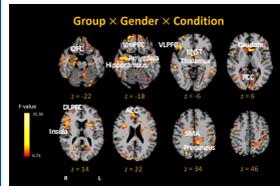


Stress Ratings



Higher alcohol cue-induced craving was found in HB drinkers relative to LM drinkers across men and women. Higher stress ratings were found in women compared to men, especially in female HB drinkers.

fMRI Results



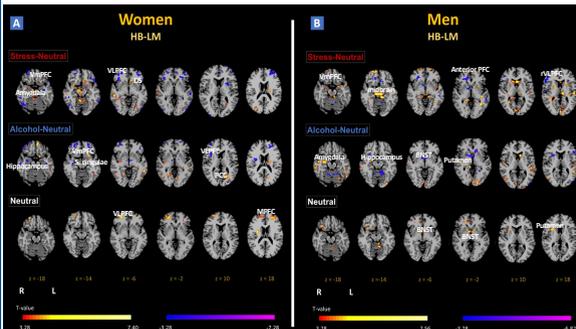
Group x Gender x Condition

- Group (HB, LM)
- Gender (men, women)
- Condition (stress, alcohol-cue, neutral)

An interaction effect was found in

- prefrontal cortex (PFC): OFC, vmPFC, VLPFC, DLPFC
- limbic-striatal regions: striatum (caudate), amygdala, hippocampus
- insula, precuneus, SMA, BNST, and thalamus

Group-specific differences



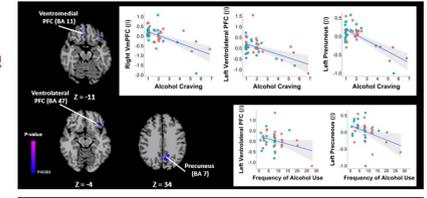
In women:

- S-N: Hypoactivity in the vmPFC, VLPFC but hyperactivity in the amygdala, and dorsal striatum (DS) in HB vs. LM.
- A-N: Hypoactivity in the vmPFC, VLPFC, hippocampus; hyperactivity in the subgenual cingulate (S. cingulate), PCC in HB vs. LM.
- Neutral: Increased PFC activity in the VLPFC and MPFC in HB vs. LM

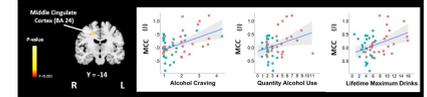
In men:

- S-N: Hypoactivity in the vmPFC, VLPFC but hyperactivity in the anterior PFC, DS, midbrain in HB vs. LM
- A-N: Hypoactivity in the putamen, BNST but hyperactivity in the amygdala, hippocampus in HB vs. LM
- Neutral: Increased PFC, DS, and BNST activity in HB vs. LM.

Women



Men



- **in women:** during the alcohol cue condition,
 - Decreased activity in the vmPFC, VLPFC, and precuneus was associated with higher alcohol craving
 - Decreased activity in the VLPFC and precuneus was associated with higher alcohol craving (greater frequency per week)
 - Baseline alcohol consumption (average number of alcohol use and maximum drinks per month)
- **in men:** during the alcohol cue condition,
 - Increased activity in right mid cingulate cortex (MCC) was associated with higher alcohol craving
 - Baseline alcohol consumption (average number of alcohol use and maximum drinks per month)

CONCLUSIONS

- The current study identified:
- 1) sex-specific neural responses to stress and alcohol cues in risky drinkers in prefrontal-limbic-striatal regions
 - Female risk drinkers displayed:
 - decreased activity in prefrontal regions suggesting their stress and emotion regulation difficulties
 - Male risk drinkers displayed:
 - increased striatal-limbic responses suggesting their reward and impulsivity proneness
 - 2) sex-specific neural correlates of alcohol cue-induced craving and alcohol intake
 - In women: decreased activity in the vmPFC and VLPFC involved in emotion regulation¹⁰
 - In men: increased right midcingulate activity, involved in impulsivity and action¹¹
- Significance & Implications: These differential neural mechanisms may help in:
- early detection of men and women at risk for developing problematic drinking and AUD
 - developing sex-specific targeted prevention and treatment strategies for risky drinkers e.g., strategies focused on emotion regulation for women and impulse control for men

REFERENCES & ABBREVIATIONS

1. Gmelin et al. (2008). Alcohol use and burden for 195 countries and territories, 1990-2004: a systematic analysis for the Global Burden of Disease Study 2004. *The Lancet*, 370(9652), 815-823.
2. World Health Organization. (2011). *Global status report on alcohol and drug use 2011*. Geneva: World Health Organization.
3. World Health Organization. (2011). *Global status report on alcohol and drug use 2011*. Geneva: World Health Organization.
4. Sinha et al. (2015). Gender-specific patterns of alcohol use and related outcomes among heavy and moderate drinkers. *Alcohol*, 2015, 2012-2013. <https://doi.org/10.1016/j.alcohol.2015.08.004>
5. Sinha et al. (2015). Gender-specific patterns of alcohol use and related outcomes among heavy and moderate drinkers. *Alcohol*, 2015, 2012-2013. <https://doi.org/10.1016/j.alcohol.2015.08.004>
6. Sinha et al. (2015). Sex differences in neural responses to stress and alcohol cues in heavy and moderate drinkers. *Neural Science*, 11, 1-10.
7. Sinha et al. (2015). Sex differences in neural responses to stress and alcohol cues in heavy and moderate drinkers. *Neural Science*, 11, 1-10.
8. Sinha et al. (2015). Sex differences in neural responses to stress and alcohol cues in heavy and moderate drinkers. *Neural Science*, 11, 1-10.
9. Sinha et al. (2015). Sex differences in neural responses to stress and alcohol cues in heavy and moderate drinkers. *Neural Science*, 11, 1-10.
10. Sinha et al. (2015). Sex differences in neural responses to stress and alcohol cues in heavy and moderate drinkers. *Neural Science*, 11, 1-10.
11. Sinha et al. (2015). Sex differences in neural responses to stress and alcohol cues in heavy and moderate drinkers. *Neural Science*, 11, 1-10.
- Abbreviations:
- HB: heavy-binge drinkers
 - LM: light-to-moderate drinkers
 - vmPFC: Ventromedial prefrontal cortex
 - VLPFC: ventrolateral prefrontal cortex
 - vLPFC: right Ventrolateral prefrontal cortex
 - PCC: Posterior cingulate cortex
 - ACC: Anterior cingulate cortex
 - OFC: Orbitofrontal cortex
 - DLPFC: Dorsolateral prefrontal cortex
 - VLPFC: ventrolateral prefrontal cortex
 - SMA: Supplementary motor area
 - BNST: Bed nucleus of the stria terminalis