Unique associations between insular alcohol cue reactivity and naturalistic drinking outcomes among individuals with alcohol use disorder

Sydni Anderson, BS, & William Mellick, Ph.D.
Charleston Alcohol Research Center, Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina, Charleston, SC

BACKGROUND

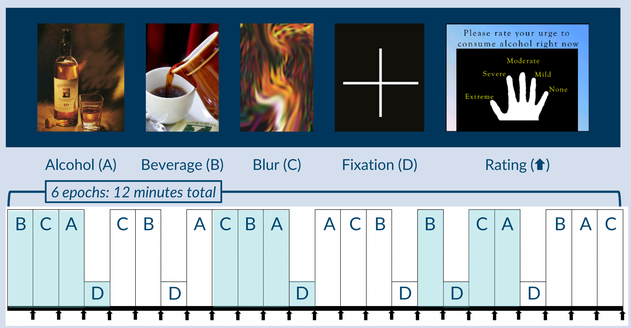
- Alcohol cue reactivity assessed through functional magnetic resonance imaging (fMRI) is strongly associated with measurements of alcohol use[1].
- Cue reactivity studies of individuals with alcohol used disorder (AUD) have identified neural substrates associated with AUD maintenance factors (e.g., craving; insula)[2] and relapse (e.g. ventral striatum)[3].

AIM

To identify potentially unique relations between cue reactivity and self-reported naturalistic drinking associated with AUD.

METHODS

- 28 individuals were recruited to form AUD and healthy control groups (HC).
- Participants completed self-report measures of craving (OCDS), alcohol dependence (ADS), and sensitivity to punishment and reward (SPSR-Q); and underwent clinical interviews, including timeline followback (TLFB), and a fMRI scanning protocol including a well-validated visual alcohol cue reactivity paradigm.
- Regions-of-interest (ROI): right medial prefrontal cortex (RmPFC), left ventral striatum (LVS), and left insula.
    - % signal change was extracted from 8-mm radius spherical ROIs using MarsBaR toolbox from SPM12.
- Bivariate associations between key variables were analyzed to inform selection of exploratory moderation models (at a nominal $p < 0.05$).



1 epoch (2 min.) = 4 blocks in pseudorandom order; each category block includes 5 pictures (4.8s/picture) followed by an "urge to drink alcohol" handpad rating (6s).

Figure 1. Alcohol cue reactivity paradigm

RESULTS & CONCLUSIONS

Variables [x̄ (SD) or %]	AUD (n=14)	HC (n=14)	t/χ^2 (p)*
Age	32.79 (±10.50)	35.86 (±12.04)	-0.719 *(0.478)*
Sex (% female)	35.71%	50.00%	0.583 *(0.704)*
Smoking (% smokers)	21.43%	0%**	4.167 *(0.347)*
ADS	9.57 (±4.60)	1.36 (±1.55)	6.328 *(< 0.001)*
OCDS Total	7.85 (±4.93) ‡	3.07 (±2.09)	3.232 *(0.005)*
Drank w/in 2 weeks of scan	92.86%	92.86%	0 *(0.999)*
# Drinks/drinking day	7.13 (±2.70)	1.87 (±0.63) ‡	7.096 *(0.001)*
% HDD	43.99% (±30.21%)	3.74% (±6.35%)	4.879 *(< 0.001)*
% Days abstinent	29.57% (±23.79%)	62.38% (±22.28%) ‡	-3.692 *(0.001)*

Table 1. Participant characteristics

ADS, Alcohol dependence scale; OCDS, Obsessive compulsive drinking scale; HDD, heavy drinking days
*Cohen's D effect sizes were large for drinking variables, min: 1.16, max: 2.64
**1 former smoker
†Past 90 days, per TLFB
‡n=13, due to elimination of significant outliers or incomplete data

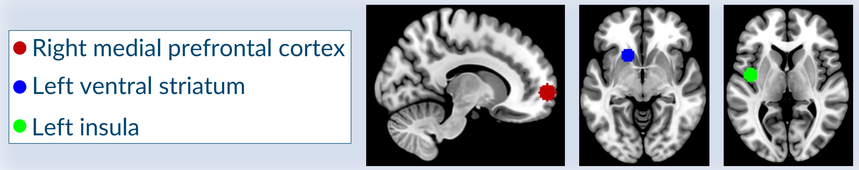


Figure 2. Regions of interest (ROIs)

MNI space coordinates: RmPFC (x = 12, y = 62, z = 0), LVS (x = -16, y = 16, z = -8), and left insula (x = -41, y = -5, z = 6)

	R (p)	Right mPFC	Left VS	Left Insula
AUD (n=14)	OCDS Total	0.16 *(0.593)*	0.44 *(0.132)*	0.12 *(0.714)*
	SR	0.13 *(0.657)*	0.75 *(0.002)***	0.04 *(0.892)*
	# Drinks/drinking day†, ‡	0.08 *(0.775)*	0.45 *(0.110)*	0.25 *(0.405)*
	% HDD†	0.35 *(0.218)*	0.33 *(0.252)*	0.70 *(0.008)***
	% Days abstinent†, ‡	-0.48 *(0.081)**	-0.29 *(0.316)*	-0.73 *(0.005)***
HC (n=14)	OCDS Total‡	-0.11 *(0.711)*	0.02 *(0.950)*	-0.17 *(0.569)* ‡
	SR	0.18 *(0.531)*	-0.02 *(0.936)*	-0.44 *(0.116)* ‡
	# Drinks/drinking day†	0.51 *(0.074)**	0.54 *(0.059)**	-0.35 *(0.238)* ‡
	% HDD†	0.25 *(0.399)*	0.30 *(0.296)*	-0.05 *(0.858)* ‡
	% Days abstinent†	-0.04 *(0.909)*	-0.01 *(0.974)*	-0.11 *(0.720)* ‡

Table 2. Associations between cue reactivity and behavioral correlates

mPFC, medial prefrontal cortex; VS, ventral striatum; OCDS, Obsessive compulsive drinking scale; SR, reward sensitivity from SPSR-Q
*p < 0.10
**p < 0.05
†Past 90 days, per TLFB
‡n<14, due to elimination of significant outliers or incomplete data

- Correlations showed significant strong positive associations between insular activation to alcohol cues and heavy drinking **(Table 2)**. AUD showed a significant positive moderating effect on this relationship with respect to %HDD along with a significant negative moderating effect with respect to %days abstinent **(Figure 3).**
- Correlations between cue reactivity in the LVS and RmPFC and key variables were not significant **(Table 2)** and moderation models did not indicate differential influence by AUD.

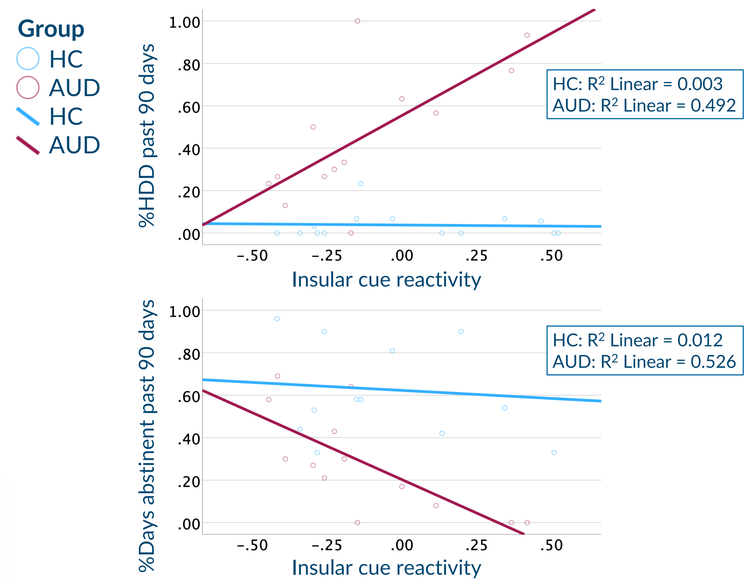


Figure 3. Moderation models of AUD on insular cue reactivity and drinking outcomes

Moderation models between insular cue reactivity and # drinks/drinking day were non-significant.

Conclusions:

- The findings suggest a unique association between insular alcohol cue reactivity and drinking habits among AUD individuals, reinforcing the insula's role as a salience network "hub," coordinating motivated goal-directed behaviors (e.g. compulsive drinking).
- Correlation between VS cue reactivity and reward sensitivity (SR) was strong and significant in AUD individuals, consistent with literature linking SR to alcohol-related problems[4].
- Lack of association between cue reactivity and craving (OCDS) was unexpected but may be explained by distinct mechanisms of "baseline" and cue reactivity craving[5].
- A trend association between number of drinks per drinking day and RmPFC cue reactivity in healthy controls, along with negative association with percent days abstinent in AUD, may reflect alterations in cue processing associated with transition from reward-based drinking to alcohol dependence[6].
- The insula shows promise as a brain stimulation target in treatment studies on substance use disorders,[7,8] though more research is needed to establish the use and efficacy of this treatment model among AUD individuals.

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