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ARTICLE

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High-intensity sweet taste as a predictor of subjective alcohol responses to the ascending limb of an intravenous alcohol prime: an fMRI study

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High-intensity sweet-liking has been linked to alcohol use disorder (AUD) risk. However, the neural underpinning of this association is poorly understood. To find a biomarker predictive of AUD, 140 participants (social and heavy drinkers, ages 21–26) underwent functional magnetic resonance imaging (fMRI) during a monetary incentive delay (MID) task and stimulation with high ($Sucrose_{High}$)- and low-concentration sucrose, as well as viscosity-matched water. On another day after imaging, and just before free-access intravenous alcohol self-administration, participants experienced a 30 mg% alcohol prime (10 min ascent) using the Computerized Alcohol Infusion System. Principal component analysis (PCA) of subjective responses (SR) to the prime's ascending limb generated enjoyable (SR_{enjoy}) and sedative (SR_{sed}) intoxication components. Another PCA created one component reflective of self-administered alcohol exposure (AE) over 90 min. Component loadings were entered as regressors in a voxel-wise general linear fMRI model, with reward type as a fixed factor. By design, peak prime breath alcohol concentration was similar across participants (29 ± 3.4 mg%). SR_{enjoy} on the prime's ascending limb correlated positively with [$Sucrose_{High}$ > Water] in the supplementary motor area and right dorsal anterior insula, implicating the salience network. Neither SR component correlated with the brain's response to MID. AE was unrelated to brain reward activation. While these findings do not support a relationship between alcohol self-administration and (1) subjective liking of or (2) regional brain response to an intensely sweet taste, they show that alcohol's enjoyable intoxicating effects on the rising limb correspond with anterior insular and supplementary motor area responses to high-concentration sucrose taste. No such associations were observed with MID despite robust activation in those regions. Insula and supplementary motor area responses to intense sensations relate to a known risk factor for AUD in a way that is not apparent with a secondary (monetary) reward.

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INTRODUCTION

Sweet-liking has been linked to alcohol consumption and AUD risk in both humans and animals [1, 2], but with less attention to related brain mechanisms. We initially reported that daily drinking intensity was associated with greater orbitofrontal activation [3] from high-concentration sucrose—a finding that did not survive in a larger sample [4]. Rudenga and Small [5] also showed no association between the brain response to sweet taste and self-reported alcohol use. However, self-reported drinking can vary across participants [6] and its temporal resolution for subjective response (SR) to alcohol exposure is poor. We therefore employed laboratory-based alcohol self-administration to examine the relationship between the brain's response to sweet taste and SR to alcohol.

Both consummatory (e.g., sweet taste, alcohol) and abstract rewards (such as money) engage common brain systems [7, 8], but with key differences [9]. Thus, while reward mechanisms in AUD have been studied using mostly monetary reward tasks, a salient consummatory reward could offer greater external validity for investigating brain mechanisms underlying alcohol use. In fact, some argue that a similar brain response across consummatory rewards reflects a mechanism for transference of reward drive between sweet rewards and alcohol [2, 10]. Thus, we posit that the neural processing of sweet rewards may better parallel those of alcohol reward and therefore prove a useful surrogate.

While the relationship between sweet and alcohol reward is poorly understood, that between SR to alcohol exposure and AUD risk is better studied. Schuckit, et al. [11] first reported that the sons of fathers with AUD had greater tolerance to alcohol's adverse effects and were more likely to develop future alcohol problems. Recently, King et al. [12] showed that greater sensitivity

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to alcohol's pleasant effects was related to future AUD. Both findings relate to Newlin and Thomson's "differentiator" model [13], which hypothesizes that a predisposition to AUD includes sensitivity to alcohol's pleasant effects during the rising limb (ascent) in breath alcohol (BrAC) and resistance to the aversive effects on the descending limb.

To clarify brain mechanisms that mediate alcohol reward-sensitivity and sweet-liking, we tested for associations between SR to alcohol and brain responses to sweet taste (primary reward), as well as both secondary reward anticipation and receipt using the monetary incentive delay (MID) task. We employed the laboratory-based computerized alcohol infusion system (CAIS; [14]), which permits ad libitum intravenous alcohol self-administration using individual physiologically-based pharmacokinetic modeling to standardize each BrAC increment and avoid the inter-individual BrAC variability inherent to oral consumption [15, 16]. Intravenous administration also separates intoxicating effects from confounding rewarding sensations, such as flavor [17].

We tested four hypotheses: (1) Participants who like intensely sweet tastes self-administer a greater alcohol-exposure and (2) responses to an intensely sweet taste in reward-related brain areas positively predict self-administration. (3) Reward region responses to an intensely sweet taste correlate with SR change on alcohol's ascending limb. (4) The association between reward-related brain response and SR is specific to primary (consummatory) rewards (sweet taste) and absent from monetary reward.

METHODS

Procedures

Interview, MRI, and alcohol self-administration occurred on separate days (Figs. S1–S3). Assessments included the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; [18]), a 35-day version of the Timeline Followback interview [19], the revised NEO-Personality Inventory (NEO; [20]), the Center for Epidemiological Studies-Depression Scale (CES-D; [21]), the Short Urgency, (lack of) Premeditation, (lack of) Perseverance, and Sensation seeking Personality scale (SUPPS-P; [22]), and the Alcohol Use Disorders Identification Test (AUDIT; [23]). Procedures occurred only following participants' written consent approved by the Indiana University IRB.

Participants

One hundred seventy-two healthy participants (a subsample of whom were reported previously [4]) were balanced by family history of AUD, recent drinking, and sex (supplement for inclusion/exclusion criteria). Eight were excluded for incomplete imaging, excessive motion, or technical problems prior to data quality review, described below. A further 21 were excluded for incomplete alcohol self-administration data from not returning for the session ($n = 3$), insufficient alcohol supply ($n = 4$), nausea/investigator concerns about safety ($n = 8$), intravenous insertion site problems ($n = 2$), or technical problems ($n = 4$). Three had data quality problems involving both self-administration and imaging.

The family history assessment module [24] of the SSAGA [18] interview determined family history status, with family history negative (FHN) defined as no first- or second-degree relatives with AUD. Family history positive (FHP) status required at least one first-degree relative with AUD. Those with a maternal history of AUD ($n = 11$) reported that their mothers abstained during pregnancy ($n = 7$) or that alcohol problems were postnatal ($n = 5$; i.e., one reported both). The final sample (Table 1) included 140 participants; 71 (50.7%) were female, and 66 (47.1%) family history positive. Family history groups did not differ in average drinks per week, average drinks per drinking day, or sex [$\chi^2 = 0.27$] ($ps > 0.46$).

Table 1. Participant characteristics ($N = 140$).

	Mean (SD)	Percent (*N*)
Age	22.5 (1.5)	
Male		49% (69)
Education	15.2 (1.2)	
White		84.3% (118)
Non-Hispanic		96.4% (135)
Positive Family History		47.1% (66)
Drinks/Drinking day	4.2 (2.5)	
Drinks/week	10.0 (8.6)	
AUDIT	8.6 (4.5)	
Alcohol Use Disorder Positive		35% (49)

Recruitment aimed to balance groups by sex (M/F), drinking (Social vs Heavy; 14 (if male) or 7 (if female) drinks/week cutpoint), and family history of AUD. Individuals were included only if they had at least one first-degree relative with a family history of AUD OR no relatives with AUD. All participants were right-handed. AUD positive reflects DSM5, 2+ lifetime diagnostic criteria as recoded from the Semi-Structured Assessment for the Genetics of Alcoholism interview.
SD standard deviation, *N* count.

Imaging day

Taste test. Before imaging, participants rated perceived intensity and pleasantness of five concentrations of sucrose-sweetened water. Intensity ratings used a labeled magnitude scale [25] and pleasantness used a visual analog scale. Solutions were presented in three blocks of five volumes, with order in each block pseudorandomized and participants blind to order and concentration (range 0.05 M to 0.83 M). Participants were given 15 mL of each solution in a cup and instructed to "swish" for 5 s and spit without swallowing. Following ratings, participants cleansed their palates using ~10 mL of deionized water before the next cup.

Sucrose stimulation task (fMRI). A mouthpiece delivered tastant sprays from a computer-controlled five-channel gustometer [3, 26]. In six functional scans, three solutions were delivered: a 0.1 M (low) sucrose solution ($Sucrose_{Low}$), a 0.83 M (high) sucrose solution ($Sucrose_{High}$), and a water control. $Sucrose_{Low}$ and water were viscosity-matched to $Sucrose_{High}$ using a tasteless thickening agent (ThickenUp Clear®, Nestlē Health Sciences, Vevey, Switzerland). $Sucrose_{High}$ and $Sucrose_{Low}$ were delivered in separate, alternating scans (3 each), with water as an activated baseline control (Fig. S4 and [3, 4] for detail). Participants were randomized to scan order, balancing across family history and drinking groups.

Monetary incentive delay task (fMRI). Participants performed the monetary incentive delay (MID; Fig. S5) task [27]. A cue signaled the ability to win (Win) or avoid losing one or five (5) dollars (Win5; Fig. S5) by responding during a reaction time target's display. A neutral cue signaled a control trial without monetary gain/loss. The task adjusted reaction time to approximate 66% accuracy for each trial type. After each trial, participants received performance feedback (trial outcome plus cumulative winnings). Participants practiced a shortened task outside the scanner before imaging. Winnings were paid at the end of the study day.

Image acquisition and analysis. Imaging used a Siemens 3T Magnetom Prisma (Erlangen, Germany) scanner and a 64-channel head coil array. Blood oxygenation level dependent (BOLD) contrast-sensitive images were acquired using a product echo planar imaging (EPI) sequence (gradient echo, repetition/echo time (TR/TE) 2110/29 ms, flip angle 78°, field-of-view $220 \times 220\ mm^2$, matrix 80×80, 39 interleaved 3 mm thick slices, $2.75 \times 2.75 \times 3.0\ mm^3$ voxels, GRAPPA acceleration factor 2, 164 measurements). A high-resolution anatomical image ($1.05 \times 1.05 \times 1.2\ mm^3$ voxels, T1-weighted 3D magnetization prepared rapid gradient echo) was acquired for co-registration with the BOLD images. Functional imaging included one MID task and six sucrose stimulation BOLD fMRI scans, brief instructions, intra-MRI assessment questions, and time for post-scan water rinse delivery and post-scan subjective ratings (~65 min). Prior to the MID and sucrose scans, a gradient echo field mapping scan (TR = 355 ms, TE1/TE2 = 3.86/6.32 ms, advanced B0 shim mode adjustment, same imaging volume and voxel size as BOLD EPI) optimized field homogeneity and facilitated BOLD EPI volume distortion evaluation/correction. Foam pads and real-time prospective acquisition motion correction reduced head movement [28].

Image preprocessing used the FMRIB Software Library (FSL version 6.0; [29], including BOLD volume geometric distortion correction with *fugue* that utilized distortion field estimates from a field mapping scan, slice time acquisition correction with *slicetimer*, motion correction with *mcflirt* [30],

brain extraction with *bet* [31], registration to each participant's T1-weighted image and MNI152 standard space with *flirt* and *fnirt*, and 6 mm FWHM Gaussian filter spatial smoothing. FSL's MELODIC version 3.15 automatically estimated and retained an optimal number of independent components for each BOLD scan, which was subsequently denoised using an unsupervised ICA-AROMA [32] classifier. Denoised data were projected into standard MNI space and interpolated to 2 mm isotropic voxels for statistical analyses.

Given potential effects from swallowing during sucrose fMRI, quality control (QC) screening (blind to participant characteristics) assessed both [Sucrose>Implicit Baseline] activation in primary somatosensory cortex from the intraoral stimulation (Figs. S9–S11) and excessive activation within the cerebrospinal fluid and/or white matter. To maximize sample size and include the same number of sucrose scans for each participant, we included only two QC-verified sucrose scans at each concentration for each participant. Considering potential habituation in those with three QC-verified scans at each concentration, we counter-balanced scan-pair orders (i.e., first/second, first/third, second/third) across family history, sex, and drinking groups. Five participants failed QC criteria for $Sucrose_{High}$ scans and two participants for $Sucrose_{Low}$ scans resulting in a total of seven participants excluded from analyses of both concentrations.

Intravenous alcohol self-administration paradigm

Alcohol sessions began with a 30-min "prime" immediately followed by 90 min ad libitum alcohol self-administration. CAIS [15] allowed participants to choose an intravenous "drink" (described as "bits" to avoid implying a drinking glass volume) by depressing a button, with each press raising BrAC by a targeted 7.5 mg% over 2.5 min [14]. During this 2.5 min, the button was inactive, and the screen displayed a message that the bar was closed.

The prime began with participants being asked to depress the button four consecutive times to achieve a targeted peak BrAC of ~30 mg% in 10 min. Following this ascent, alcohol became unavailable for 20 min and CAIS maintained a controlled linear descent of ~1 mg/dl/min to reach 10 mg% BrAC. Ad libitum self-administration immediately followed. Breath readings occurred near the peak of every self-administration for the first six requests and then every other request for feedback. This generated a latent BrAC curve throughout the session, up to a 150 mg% maximum safety limit when the "bar-closed" message appeared until BrAC declined.

Participants rated on a visual analog scale subjective enjoyment, sedation, anxiousness, stimulation, intoxication, and fatigue (each defined using synonyms; Supplementary Materials and Methods). Participants also rated perceived number of drinks (to the nearest ½ drink) from 0 to 10 + . Ratings occurred at baseline just prior to the prime, at the estimated prime peak, prime end, and at 20-minute intervals during self-administration near a local peak when applicable. Question order was randomized at each acquisition.

Statistical analysis

Principal component analysis. To reduce dimensionality we performed principal component analyses (PCA) with Varimax rotation [33] (SPSS 28, IBM 2021) on variables characterizing the self-administration profile and, separately, SR to the fixed 30 mg% alcohol prime exposure, retaining components with eigenvalues > 1.0 (Table S9).

Inputs for alcohol self-administration included three variables— area under the curve during self-administration, peak BrAC, and BrAC slope during the first 75 min of self-administration (time for the fastest participant to reach the 150 mg% limit).

SR variables for the prime's ascending limb to 30 mg% comprised perceived intoxication, number of drinks, enjoyment, stimulation, sedation, and tiredness (all calculated as peak—baseline). Anxiousness was excluded for zero inflation (>70% at all timepoints). Although data were acquired during self-administration, we limited SR analyses to the prime given its standard BrAC exposure across participants. PCA prerequisites were satisfied (linearity; Kaiser-Meyer-Olkin measure = 0.73 for SR and 0.59 for self-administration; Bartlett's test of sphericity, $ps < 0.001$). Higher scores reflect greater SR and self-administration. Pearson coefficients evaluated correlations between principal components.

Non-normally distributed variables. Square root transforms of drinks/drinking day and drinks/week were used in linear models.

BOLD fMRI models. Within-subject fixed effects of the BOLD response to trials were estimated in SPM12 [34] using the canonical hemodynamic response function (HRF) with time and dispersion derivatives. Sucrose and water trial onsets (duration = 3 s) coincided with pump activation. MID trial conditions modeled cue onsets, and in a separate model, feedback (wins and neutral outcomes), using only canonical HRF. Swallowing (sucrose) and button presses (MID) were conditions of no interest, using visual cue onsets. Six head motion parameters from realignment served as multiple regressors. An autoregressive AR(1) model accounted for serial correlations, while a high-pass filter (1/128 Hz) removed low-frequency noise. Contrasts of interest were $Sucrose_{High}$ relative to water, as well as Win5 relative to neutral (i.e., [$Sucrose_{High}$ > Water], [Win5 > Neutral]). Water immediately following sucrose was excluded to maximize taste contrast [4].

Contrasts were compared in group random effects one-way analysis of variance (ANOVA) models: ([$Sucrose_{High}$ > Water] vs [$Sucrose_{Low}$ > Water]), ([$Sucrose_{High}$ > Water] vs $[Win5 > Neutral]_{cue}$), and ([$Sucrose_{High}$ > Water] vs $[Win5 > Neutral]_{feedback}$). PCA-derived component weights for each participant were covariates. While the self-administration component was tested as a covariate in the same model as the SR measures, separate models compared $Sucrose_{High}$ to (1) $Sucrose_{Low}$ (2) Win5 anticipation and (3) Win5 feedback.

Per a priori hypotheses, we created an explicit mask of the frontal lobe, insula, and striatum (Harvard-Oxford parcellation, ≥99% probability; Fig. S6) as well as the pallida and amygdalae (Melbourne Subcortex Atlas Scale I [35]). The significance criterion was family-wise error-corrected (FWE) voxel-level, $p_{FWE} < 0.05$ [36], correcting for multiple comparisons within the mask volume, and minimum cluster size $k \geq 5$. Effects of interest were tested further in other statistical models by extracting mean activation from 5 mm radius spheres (Figs. S7, S8).

RESULTS

Alcohol self-administration

Ad libitum alcohol self-administration varied widely (e.g., peak BrAC Range = 14.8–154.2 mg%, average = 89.3 mg%, $n = 140$). PCA ($n = 140$) on the three self-administration variables yielded one principal component reflecting alcohol exposure (AE; Table S9), while PCA on SR revealed two principal components, interpretable as enjoyable intoxication (SR_{enjoy}) and sedative intoxication (SR_{sed}; Table S9).

SR_{enjoy} did not correlate with AE, AUDIT, drinks/week, or drinks/drinking day ($ps > 0.10$). SR_{sed} negatively correlated with AE ($r = -0.17$, $p = 0.047$), AUDIT ($r = -0.29$, $p < 0.001$), drinks/week ($r = -0.33$, $p < 0.001$), and drinks/drinking day ($r = -0.29$, $p < 0.001$). AE correlated with drinks/drinking day ($r = 0.39$, $p < 0.001$), drinks/week ($r = 0.41$, $p < 0.001$), and AUDIT ($r = 0.34$, $p < 0.001$).

AE was examined in a stepwise FHA(2) × Sex(2) × Sweet-liking(2) factorial model using as predictors SR_{enjoy}, SR_{sed}, depression, AUDIT problem subscale, SUPPS-P average urgency, anxiety, drinks/week, and drinks/drinking day. Only SR_{enjoy}, drinks/week, and drinks/drinking day explained significant variance in self-administration. Linear regression model with these three variables and 1000 bootstrap repetitions showed significant associations between all three variables and AE (SR_{enjoy} $\beta = -0.19$, $p = 0.014$, drinks/week $\beta = 0.28$, $p = 0.014$, and drinks/drinking day $\beta = 0.21$, $p = 0.048$), collectively explaining 22.4% of variance in AE.

Effect of FHA, Sweet-liking, and sex on AE, SR_{enjoy}, and SR_{sed}

One participant did not complete the taste test ($n = 139$). Forty-three percent rated the 0.83 M solution highest, qualifying as sweet-liking. Nicotine use within the last 6 weeks was unassociated with sweet-liking ($\chi^2 = 0.115$, $p = 0.74$). FHA(2) × Sex(2) × Sweet-liking(2) factorial models with SR_{enjoy}, SR_{sed}, and AE as dependent variables showed a significant main effect of Sex on SR_{enjoy} ($p = 0.05$; men higher), without other main effects. However, a significant interaction between sweet-liking and FHA ($p = 0.03$) reflected FHP sweet-likers administering *less* alcohol (estimated marginal mean (EMM) = − 0.18) than FHP sweet dislikers (EMM = 0.16) while FHN sweet-likers administered more (EMM = 0.17) than FHN sweet dislikers (EMM = − 0.23). There were no other significant interactions ($ps > 0.08$; Figs. S12, S13).

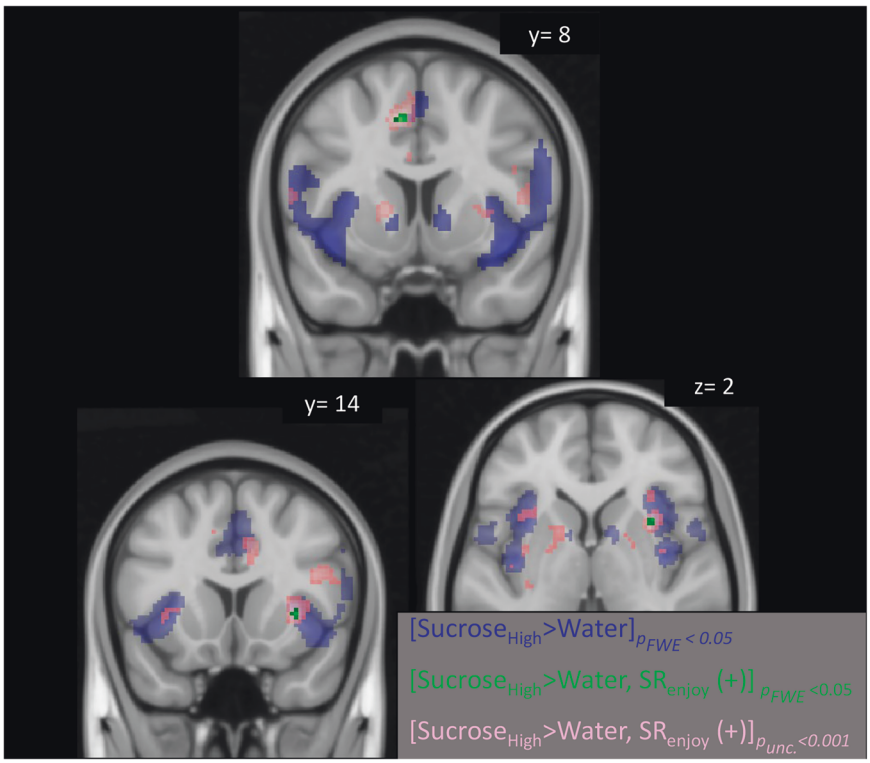

Fig. 1 BOLD activation from high-concentration sucrose (Sucrose$_{High}$) compared to water in the supplementary motor area and dorsal anterior insula correlates positively with subjective ratings of the enjoyable intoxicating effects of a fixed exposure to intravenous ethanol. Blue = Sucrose$_{High}$ greater than water activation ([Sucrose$_{High}$ > Water]). Green = [Sucrose$_{High}$ > Water] activation that predicted the enjoyable intoxicating effects of intravenous ethanol (peak-level significance $p_{FWE} < 0.05$, family-wise error corrected for the frontal/insular/striatal/amygdala/pallidal brain mask, $k = 108{,}962 = 2472.07$ cm^3; Fig. S13). Pink = the same as Green, but at $p < 0.001$ uncorrected, for context.

BOLD activation to sucrose stimulation

High-concentration sweet-taste ([Sucrose$_{High}$ > Water]) elicited robust activation in taste- and reward-related regions (Fig. 1, Table 2). The effects of [Sucrose$_{High}$ > Water] and [Sucrose$_{Low}$ > Water] were similar, apart from nonsignificant amygdala activation in [Sucrose$_{Low}$ > Water] (Table 2).

BOLD activation from either concentration versus water did not correlate with AE or SR$_{sed}$. However, [Sucrose$_{High}$ > Water] positively correlated with SR$_{enjoy}$ in both the inferior supplementary motor area (SMA; $p_{FWE} = 0.006$; $k = 9$) and dorsal anterior insula (dalNS; $p_{FWE} = 0.014$; $k = 7$). [Sucrose$_{Low}$ > Water] did not show a similar correlation. A direct comparison within 5 mm radius spheres defined by the peaks of correlation between [Sucrose$_{High}$ > Water] and SR$_{enjoy}$ showed that SR$_{enjoy}$ was significantly more associated with [Sucrose$_{High}$ > Water] than [Sucrose$_{Low}$ > Water] in both the right dalNS ($p_{FWE} < 0.001$; $k = 57$) and the SMA ($p_{FWE} = 0.008$; $k = 15$). The reverse contrast (greater correlation between SR$_{enjoy}$ and [Sucrose$_{Low}$ > Water] compared to that between SR$_{enjoy}$ and [Sucrose$_{High}$ > Water]) showed no significant foci.

BOLD activation: monetary reward compared to sucrose stimulation

Despite substantial spatial overlap between sweet ([Sucrose$_{High}$ > Water]) and monetary reward ([Win5 > Neutral]) responses (Fig. 2), MID task responses were unassociated with AE, SR$_{enjoy}$, and SR$_{sed}$.

We next tested if the correlation between the [Sucrose$_{High}$ > Water] contrast and SR$_{enjoy}$ was significantly different than correlations between [Win5 > Neutral] and SR$_{enjoy}$ by applying a small volume correction within two 5 mm radius spherical ROIs defined by the peaks of correlation between [Sucrose$_{High}$ > Water] and SR$_{enjoy}$. Both the [Sucrose$_{High}$ > Water] and [Win5 > Neutral]$_{cue}$ contrasts produced significant activation in the dalNS ($ps_{FWE} < 0.001$, $ks \geq 40$) and SMA ($ps_{FWE} < 0.001$, $ks \geq 24$), while [Win5 > Neutral]$_{feedback}$ was significant only in the dalNS ($p_{FWE} < 0.001$, $k = 36$). The sucrose response was significantly greater than that from monetary reward in the dalNS when the MID was modeled at both the cue ([[Sucrose$_{High}$ > Water] > [Win5 > Neutral]$_{cue}$]; $p_{FWE} < 0.001$, $k = 50$) and feedback ([[Sucrose$_{High}$ > Water] > [Win5 > Neutral]$_{feedback}$]; $p_{FWE} < 0.001$, $k = 47$). The sucrose response was also greater than that from monetary feedback in the SMA ([Sucrose$_{High}$ > Water] > [Win5 > Neutral]$_{feedback}$, $p_{FWE} < 0.001$, $k = 60$).

Correlations between [Sucrose$_{High}$ > Water] and SR$_{enjoy}$ were greater than correlations between [Win5 > Neutral] for cue or feedback in both regions ($ps_{FWE} < 0.007$, $ks \geq 23$; Fig. 3).

Recent drinking. Given the findings, we tested if extracted activation from the insula and SMA (at the peak of the association with SR$_{enjoy}$) correlated with drinking behavior and related problems. Extracted [Sucrose$_{High}$ > Water] activity was non-significantly correlated with AUDIT ($r = 0.14$, $p = 0.099$) and at trend level with drinks/week ($r = 0.16$, $p = 0.052$) in the SMA sphere. AUDIT correlated non-significantly with [Sucrose$_{High}$ > Water] in the dalNS ($r = 0.15$, $p = 0.083$). [Win5 > Neutral]$_{cue}$ correlated non-significantly with drinks/week ($r = 0.15$, $p = 0.083$) in the SMA. There were no correlations with [Win5 > Neutral]$_{feedback}$.

Family history of AUD, Sweet-liking, and sex. Extracted spheres of mean BOLD responses in insula and SMA were analyzed in FHA(2) × Sex (2) × Sweet-liking (2) factorial models. There were no significant effects ($ps > 0.093$).

Recent nicotine use. In those without recent nicotine use ($n = 102$; Table S10), correlations between SR$_{enjoy}$ and [Sucrose$_{High}$ > Water] remained significant ($ps < 0.003$). There were no additional significant associations ($ps > 0.072$).

Table 2. BOLD results.

	Cluster size (*k*)	Peak Z	MNI coordinates (mm)		
			x	*y*	*z*
[$Sucrose_{High}$ > Water] vs [$Sucrose_{Low}$ > Water] Model					
[$Sucrose_{High}$ > Water]					
R Ventral Anterior Insula	2978	>8	38	4	−12
R Middle Dorsal Insula (Area G)		>8	38	−6	6
R Amygdala		>8	20	−2	−16
L Ventral Anterior Insula	2920	>8	−38	4	−12
L Middle Dorsal Insula (Area G)		>8	−38	−8	4
L Amygdala		>8	−20	−4	−14
R Orbitofrontal Cortex	52	>8	22	30	−18
L Orbitofrontal Cortex	103	>8	−24	34	−16
R Supplementary Motor Area	540	6.69	4	16	40
R Middle Cingulate Cortex		6.24	4	22	28
L Middle Cingulate Cortex		6.06	−2	18	34
R Ventral Striatum/Pallidum	68	6.44	10	8	0
Right posterior/middle cingulate Cortex	27	5.69	2	−16	28
L Ventral Striatum/Pallidum	25	5.61	−10	6	0
L Middle Frontal Gyrus	30	5.45	−44	40	10
R Middle Frontal Gyrus	66	5.07	44	42	6
R Middle Frontal Gyrus		5.00	44	46	14
[$Sucrose_{High}$ > Water] > [$Sucrose_{Low}$ > Water]					
R Amygdala	110	7.25	22	−2	−18
L Amygdala	99	6.94	−20	−4	−14
R Ventral Anterior Insula	5	4.83	40	8	−12
Covariate correlations					
[$Sucrose_{High}$ > Water] vs [$Sucrose_{Low}$ > Water] Model					
[$Sucrose_{High}$ > Water], SR_{enjoy} (+)					
L Supplementary Motor Area	9	5.00	−8	8	46
R Dorsal Anterior Insula	6	4.82	32	14	2
[$Sucrose_{High}$ vs Win5] Cue Model					
[$Sucrose_{High}$ > Water], SR_{enjoy} (+)					
R Dorsal Anterior Insula	13	5.20	32	14	2
L Supplementary Motor Area	6	4.88	−8	8	46
[$Sucrose_{High}$ vs Win5] Feedback Model					
[$Sucrose_{High}$ > Water], SR_{enjoy} (+)					
R Dorsal Anterior Insula	11	5.18	32	14	2

Win5 (win $5) conditions (either cue or feedback) from monetary incentive delay task ($N = 140$). All values shown are computed within the a priori conjoint binary mask comprised bilaterally of frontal lobe, insula, striatum, amygdala and pallidum. Only peaks with $p_{FWE} < 0.05$, $k \geq 5$ are displayed. Tables S1–S8 show activation in all subjects (with and without alcohol self-administration).
MNI Montreal Neurological Institute, SR_{enjoy} enjoyable component of subjective responses to alcohol, $Sucrose_{High}$ 0.83 M sucrose ($N = 140$), $Sucrose_{Low}$ 0.10 M sucrose ($N = 138$).

DISCUSSION

High-concentration sucrose, but not low-concentration sucrose or monetary reward, elicited right daINS and SMA responses that predicted alcohol's pleasant intoxicating effects. Those with greater activation to intensely sweet taste reported greater enjoyable intoxicating effects to a fixed intravenous alcohol exposure, a risk for AUD [12].

We found no association between alcohol's sedative effects and the brain response to sucrose. This is perhaps unsurprising as sucrose is an intense primary reward that would involve salience, stimulation, and reward [37], rather than sedation. Enjoyable intoxication was, however, related to $Sucrose_{High}$-induced daINS and SMA activation. The right daINS correlation with a principal component including perceived stimulation is consistent with this area's role in sympathetic autonomic sensation [38–41]. The ventral SMA neighbors the dorsal anterior cingulate considered responsible for reward-based decision-making and limbic *motor* responses [41, 42]. Both of these midcingulo-insular salience network [43] areas are implicated in addiction maintenance [44].

Moreover, the association between daINS and SMA activation and enjoyment was unique to $Sucrose_{High}$, even though $Sucrose_{Low}$ and MID reward cues evoked robust BOLD daINS activation. This 1) suggests a stimulus intensity threshold below which these regions' responses do not correlate with subjective

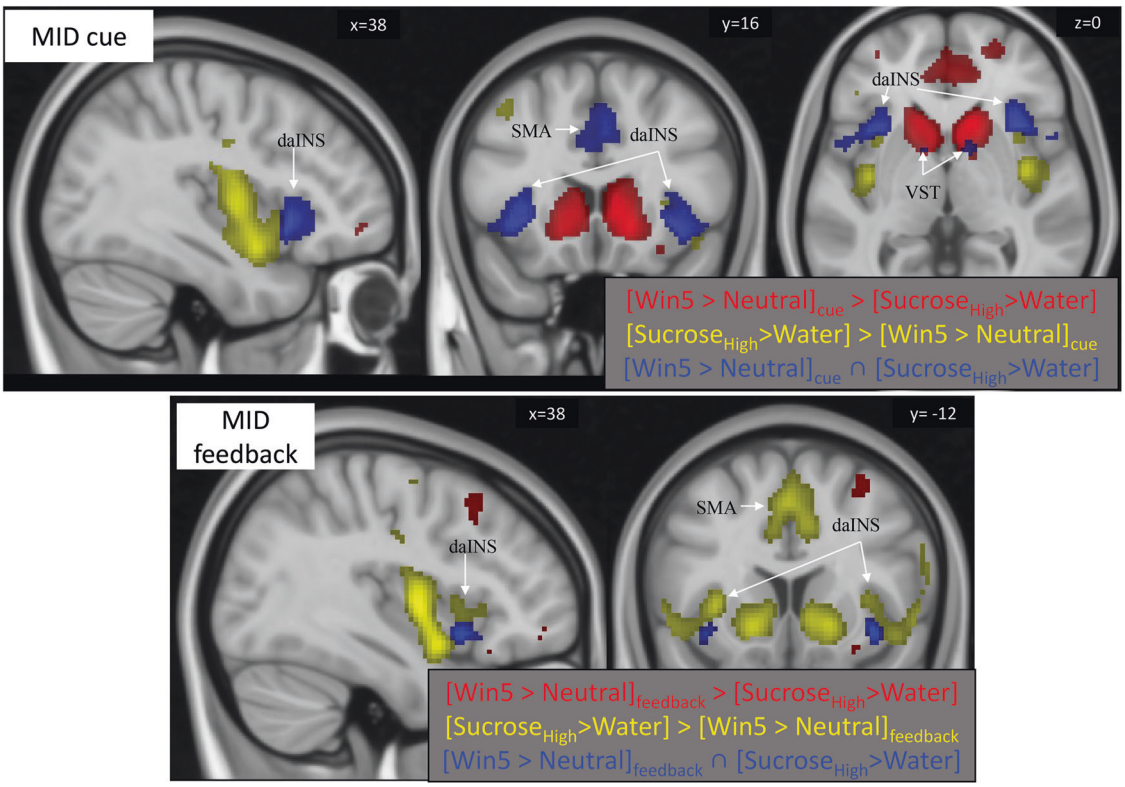

Fig. 2 BOLD activation to [Sucrose$_{High}$ > Water] and MID cued anticipation, as well as their conjunction (∩), show similar activation of the supplementary motor area (SMA) and the dorsal anterior insula (daINS). On the other hand, feedback of monetary reward receipt (successful trials) differs substantially from sucrose taste in these areas. In both cases sucrose dominates the middle insulae where the primary taste area is thought to be located (*top left*, *bottom left*). Further, although both the Win5 cue and Sucrose$_{High}$ activate the ventral striatum (VST), Sucrose$_{High}$ activation is more circumscribed, while the Win5 cue activates the striatum broadly (*top right*). By the time of Win5 successful feedback, the striatum is less active than during sucrose administration. Threshold for all contrasts shown is $p_{FWE} < 0.05$.

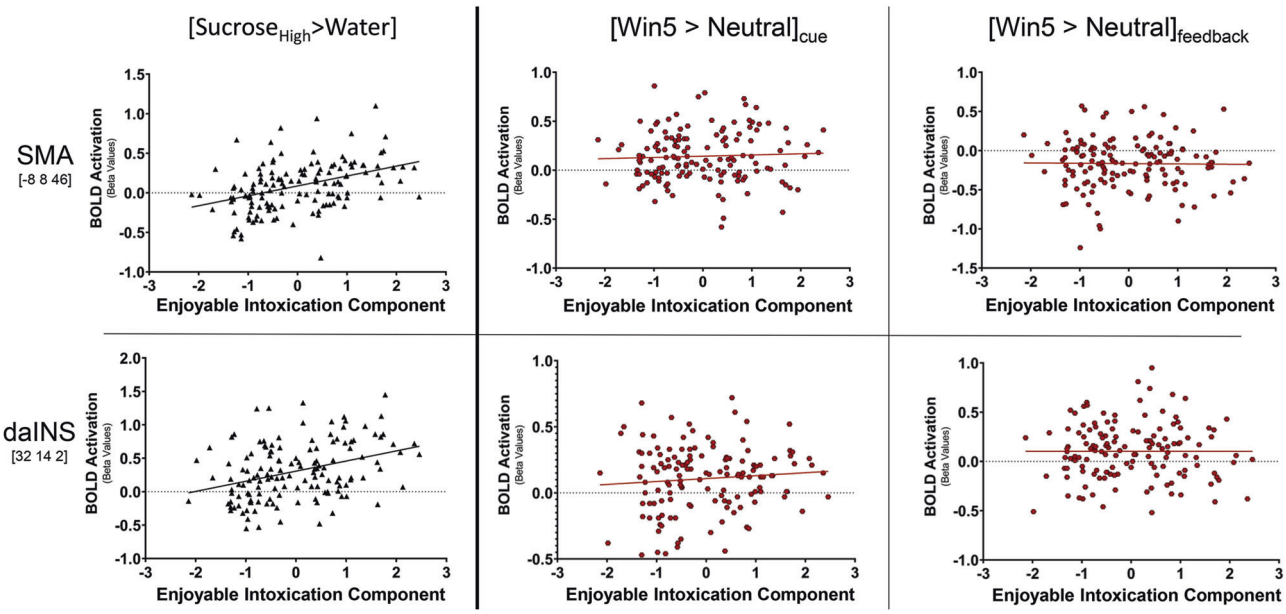

Fig. 3 Correlations between enjoyable intoxication from alcohol and response to supplementary motor area (SMA, *top*) and dorsal anterior insula (daINS, *bottom*) BOLD activation from high-concentration sucrose ([Sucrose$_{High}$ > Water], *black triangles, left*) and high monetary reward ([Win5 > Neutral]$_{cue}$ and [Win5 > Neutral]$_{feedback}$; *red circles*) vs their respective controls, with monetary reward contrasts at the times of reward cues (*center*) and feedback (*right*). Data points represent subject-level average BOLD activation extracted from 5 mm radius spheres centered on the peaks of correlation between [Sucrose$_{High}$ > Water] and the enjoyable intoxication component (SR$_{enjoy}$) from the principal component analysis.

response to alcohol, even when activation is prominent and 2) illustrates the potential importance of reward type in understanding brain markers of AUD risk. As noted by Sescousse and colleagues [9], regional responses to food and money differ [9] despite overlap [7, 45–47].

As above, both the daINS and ventral SMA are nodes of the salience network [48] that is implicated in AUD risk [44, 47, 49–51], and where lesions can result in addiction remission [44, 51]. This network is thought to orient individuals to external stimuli [52–54], with the daINS serving as a hub between multiple functional networks [38, 55–57]. It is also thought to integrate internal states with external stimuli to evaluate their relevance [38, 40], thus maintaining allostasis by comparing predicted and actual states [58], and directing organisms toward or away from stimuli to match a predicted outcome.

In particular, Feldman-Barrett and Simmons [59] proposed a predictive interoceptive model in which the anterior insula and cingulate's agranular/dysgranular cortices hold predictions that are compared to sensory information in granular cortices. When afferent information differs from the prediction, mechanisms 1) move or change body states to align the afferent information to the prediction, 2) reinterpret the sensory input, or 3) alter the prediction in a Bayesian manner. These authors suggest that the relative lack of granular cells in these areas increases the inertia of the predictions so that signals from the afferent granular regions are altered more often while the prediction is unchanged. Our results could then reflect a process in which intense sensory stimuli induce a body state that deviates from the allostatic prediction. This discrepancy could then increase salience region activity as they move to align sensation and prediction.

Our findings add to mixed results for sweet-liking, familial AUD, and drinking [2, 60–69]. We found no main effects of family history or sweet-liking on self-administration, but family history interacted with sweet-liking: FHP sweet-likers administered *less* alcohol than FHP sweet-dislikers (and vice-versa for FHN). Sweet-liking was also unassociated with recent drinking or family history. This is inconsistent with findings where FHP sweet-likers drink more than FHP sweet-dislikers [70], and where sweet-liking is a heritable trait linked with AUD [2, 61, 64, 69, 70]. Our recruitment strategy of balancing family history by recent drinking may explain the discrepancy.

Alcohol self-administration's external validity [71–75] was evident in its association with recent drinking, while the prime's sedative effects inversely correlated with subsequent self-administration, recent self-reported drinking, and problematic drinking. Enjoyable intoxication was, however, negatively related to self-administration only when covarying for recent drinking, when the association between sedation and self-administration was no longer statistically significant. This implies that those less sensitive to the intoxicating effects of alcohol's rising limb, whether from acquired or innate tolerance, subsequently administer more. While Newlin & Thomson's differentiator model [13] would seemingly suggest the opposite, their model did not propose controlling for recent drinking history, nor did it rely on data from the same principal component used here. Similarly, Schuckit's [11] Low Level of Response Model appears a better fit for these data, but Schuckit again asked different questions (body sway, high, etc..), and used an alcohol challenge method that would cause wide variation in brain alcohol exposure level and slope at measured time points [17].

In distinction to our result, meta-analyses show stimulation is positively related to recent drinking [76], with longitudinal studies [12, 77, 78] showing that stimulation from an 80 mg% BrAC oral challenge predicts binge drinking and AUD progression. Here again, SR_{enjoy} was more complex than stimulation alone, and its relationship to intravenous self-administration during this one session may not reflect broader drinking patterns as they evolve over time. In that regard, not only is route of administration different (including effects of flavor, gastric sensation, cephalic phase of ingestion, first-pass metabolism, etc.), but level of exposure (80 mg% target vs. 30 mg%) and environment (living room-like vs. hospital room) are differences that could contribute to the discrepant results.

Study limitations

We used only sweet solutions and cannot confirm if our findings are sweet-specific or if other intense tastes (e.g., bitter, umami) would show similar associations. This relationship may also not be specific to gustation. Our prime was modest in magnitude, complicating comparisons to higher oral alcohol challenges (e.g., 80 mg%). Interesting trends reflected correlations between $Sucrose_{High}$-induced right daINS and SMA responses and problematic drinking. However, the cross-sectional design cannot determine if this is a cause or consequence of alcohol consumption, or if it predicts future AUD. Due to time constraints, our fMRI paradigm included only two concentrations of oral sucrose administration, making it impossible to assess effects from intermediate concentrations.

CONCLUSION

daINS and SMA responses to a highly intense sweet taste are associated with self-reported enjoyable alcohol intoxication, a known risk for AUD. This association was not evident with a mildly sweet taste or monetary reward. Our data do not, however, support hypotheses about relationships between alcohol self-administration and (1) liking of and (2) regional brain responses to an intensely sweet taste. Future research into brain processing of other primary rewards could be useful, with potential as a biomarker that scales with enjoyable intoxication, and which can be used in children.

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AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: DAK, MD, JH, SJO'C, AEKK; data collection: GC, KB; analysis and interpretation of results: JPA, DAK, MD, GC, KB. Draft manuscript preparation: JPA, MD, DAK. All authors reviewed the results and approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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