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Family history of alcoholism and the human brain response to oral sucrose

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ABSTRACT

A heightened hedonic response to sweet tastes has been associated with increased alcohol preference and alcohol consumption in both humans and animals. The principal goal of this study was to examine blood oxygenation level dependent (BOLD) activation to high- and low-concentration sweet solutions in subjects who are either positive (FHP) or negative (FHN) for a family history of alcoholism. Seventy-four non-treatment seeking, community-recruited, healthy volunteers (22.8 ± 1.6 SD years; 43% men) rated a range of sucrose concentrations in a taste test and underwent functional magnetic resonance imaging (fMRI) during oral delivery of water, 0.83 M, and 0.10 M sucrose. Sucrose compared to water produced robust activation in primary gustatory cortex, ventral insula, amygdala, and ventral striatum. FHP subjects displayed greater bilateral amygdala activation than FHN subjects in the low sucrose concentration (0.10 M). In secondary analyses, the right amygdala response to the 0.10 M sucrose was greatest in FHP women. When accounting for group differences in drinks per week, the family history groups remained significantly different in their right amygdala response to 0.10 M sucrose. Our findings suggest that the brain response to oral sucrose differs with a family history of alcoholism, and that this response to a mildly reinforcing primary reward might be an endophenotypic marker of alcoholism risk.

1. Introduction

Sweet taste is a primary reward of evolutionary importance in helping mammals readily identify sources of energy rich carbohydrates. The reinforcing aspects of sweet taste are mediated by reward-related neurotransmitters, including serotonin, endogenous opiates, and dopamine—those also thought to communicate the rewarding properties of abused drugs (Carroll et al., 2008; Fortuna, 2010). A number of animal studies show that the preference for alcohol and other drugs of abuse is accompanied by a greater preference for sweetened stimuli (Eiler 2nd et al., 2005; Kampov-Polevoy et al., 1999; Sinclair et al., 1992). This relationship is genetically based, as animals bred for saccharin preference self-administer abused drugs more than their non-prefering littermates (Carroll et al., 2002; Dess et al., 1998). Similarly, rodents bred for alcohol preference exhibit a greater preference for sweetened solutions (Belknap et al., 1993; Eiler 2nd et al., 2005; Oberlin et al., 2011; Sinclair et al., 1992; Woods 2nd et al., 2003).

Some evidence also suggests that humans who abuse drugs,

including alcohol, have a greater preference for highly sweet solutions (e.g., Janowsky et al., 2003; Kampov-Polevoy et al., 2001; Pomerleau et al., 1991; Weiss, 1982). All such alcohol-related studies presented subjects with a range of molar (M) sucrose concentrations, most commonly in five solutions between a low of 0.05 M and peak of 0.83 M. An individual is then typically defined as a “sweet-liker” when his or her visual analog scale liking ratings are greatest at the highest (0.83 M) concentration, which is greater than the original criterion of 0.3 M established by Thompson et al. (1976). For context, 0.83 M sucrose equates to approximately 2.5 times the sweetness of Coca Cola Classic® (Coca Cola Company, Atlanta, GA). Applying this sweet-liking classification method, studies in middle-aged men show that there are a greater proportion of “sweet-likers” in those treated for alcohol dependence when compared to non-dependent controls (Kampov-Polevoy et al., 1998; Kampov-Polevoy et al., 2001; Krahn et al., 2006). Greater alcohol-related problems in non-dependent men and women college students have also been associated with being a sweet-liker (Lange et al., 2010). Nonetheless, two studies using similar methods and peak

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concentrations with comparably middle age men following alcoholism treatment have not replicated the association between alcohol dependence and sweet-liking status (Bogucka-Bonikowska et al., 2001; Wronski et al., 2007). One of these negative studies (Wronski et al., 2007) also included concentration ranges of bitter, sour, and salty tastants that could have changed the nature of the taste test. A third study that did not replicate the association between alcohol dependence and sweet-liking status (in both men and women) had patients that were significantly older (mean 48 years) than the controls (mean 26 years). These non-replicating studies also involved fewer sucrose concentrations, but this seems an unlikely explanation of the discordant findings insofar as the highest concentration (0.88 M) was quite comparable to the other studies' definitions of sweet-liking (*i.e.*, peak liking at 0.83 M).

Still, other data persist in suggesting a potential relationship between sweet-liking and alcoholism risk. Half of the variance in sweet preference is accounted for by genetic factors (Keskitalo et al., 2007). In that regard, several studies suggest that being a sweet-liker (again, as defined by liking ratings that peak at 0.83 M or 0.88 M) is more prevalent in those with a family history of alcoholism (Kampov-Polevoy et al., 2003a; Kampov-Polevoy et al., 2001; Kampov-Polevoy et al., 2003b; Lange et al., 2010; Wronski et al., 2007). Such findings suggest that sweet liking might then be an endophenotype (a hereditary characteristic associated with a condition, but not a direct symptom) for alcoholism risk. For example, one study found that a mixed sample of middle-aged male and female psychiatric and substance abuse patients with a family history of alcoholism were several times more likely to prefer stronger sweet solutions than family history negative patients (Kampov-Polevoy et al., 2003a), although sweet liking alone in this population is not *per se* predictive of diagnosed alcohol use disorder (Kampov-Polevoy et al., 2004). For example, the association between sweet liking and familial alcoholism has also been found in healthy college students without any history of a substance abuse diagnoses (Kampov-Polevoy et al., 2003a). The manifestation of this sweet preference in the absence of a diagnosed alcohol use disorder is important, as it may speak to a genetically linked endophenotype that is independent of a drug use disorder, itself. This parallels the sucrose preferences of alcohol-preferring animal lines, even prior to alcohol exposure. Some specific genetic polymorphisms may also be relevant, as the Taq 1A polymorphism of the *ANKK-1* gene might affect sweet preference in alcoholics (Jablonski et al., 2013). It should nevertheless be noted that other research does not support a link between sweet preference and familial alcoholism (Kranzler et al., 2001; Scinska et al., 2001; Tremblay et al., 2009). One of the negative studies (Tremblay et al., 2009) was age imbalanced (controls in their mid-twenties vs familial alcoholism in the upper 40's), whereas another (Scinska et al., 2001) involved subjects that were significantly younger (teens averaging 14–15) when compared to positive studies of young and older adults. The Kranzler et al. (2001) study defined sweet liking as comprising peak liking at either 0.42 M or 0.83 M, but this was not a problem with this same group's follow-up study (Tremblay et al., 2009) that used the 0.83 M peak liking criterion, and which also did not replicate the sweet-liking association with familial alcoholism.

Apart from the conflicted findings of the psychophysical studies described above, a significant gap in our understanding of the relationship between sweet taste and substance abuse lies in the extent to which the brain's reward system response to sweet taste varies as a function of alcohol use or familial alcoholism. For that reason, we have supplemented these psychophysical approaches with imaging studies of the brain response to sucrose. In a small preliminary study, we showed that orbitofrontal cortex activation to a highly sweet sucrose solution (0.83 M) positively correlated with alcohol intake, although sample size did not permit examining the influence of familial alcoholism (Kareken et al., 2013). A recent study of largely social drinkers, however, found no relation between sweet liking and indices of alcohol intake (Rudenga and Small, 2013).

In this current study, we expand on our initial findings by testing for

an association between a family history of alcoholism and the brain response to both high (0.83 M) and low (0.10 M) sucrose concentrations. Family history remains the most powerful predictive risk, as it doubles the odds of developing alcoholism (Nurnberger Jr. et al., 2004), and is thus one of the most common factors examined as an endophenotypic risk (Cservenka, 2016). We hypothesized that subjects who are positive for a family history of alcoholism (FHP), when compared to family history negative (FHN) subjects, would show a greater response to sucrose within brain regions that mediate gustation (insula/frontal operculum) and reward (ventral striatum, orbitofrontal cortex, and amygdala).

2. Materials and methods

2.1. Subjects

Seventy-four healthy, right-handed volunteers (42 women) were recruited (Table 1) and evaluated using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994), a 35-day version of the Timeline Followback interview for habitual drinking (Sobell et al., 1986), and the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993). The sample consisted of 37 FHP (defined as having at least one first-degree relative using SSAGA FHA Individual Assessment Module) and 37 FHN subjects. Subjects were excluded for histories of central neurological disease, head injury with loss of consciousness, and any DSM-IV Axis I diagnosis. Subjects were not, however, excluded for prior histories of depression and/or anxiety if not currently taking medication ($n = 8$; 2 FHP-M, 5 FHP-F, 1 FHN-F). None of the subjects expressed interest in treatment for alcohol abuse, none reported any disorders of smell or taste, and all passed an olfactory screen (Pocket Smell Test, American Version; Sensonics, Inc.). Nineteen subjects (26%; 9 FHP-M, 4 FHP-F, 4 FHN-M, 2 FHN-F) reported nicotine use within six weeks of testing (3.74 ± 2.15 units/day), 68% ($n = 13$) of whom were family history positive. Nicotine use was not related to drinking patterns. Subjects consented to a urine screen (Andwin Scientific) for commonly abused drugs [amphetamine, secobarbital, buprenorphine, oxazepam, cocaine, methylenedioxymethamphetamine, methamphetamine, morphine, methadone, opiate, oxycodone, phencyclidine, propoxyphene, and cannabinoids]; however, given its high comorbidity with alcohol, we did not exclude the one male FHN subject testing positive for marijuana use, who showed no evidence of acute intoxication, and whose last reported dose was two weeks prior to study. There was no significant difference in the brain imaging results with this subject removed. Experiments occurred only after each subject's written consent, as per the Indiana University Institutional Review Board.

2.2. Procedures

Subjects arrived at ~7:00 am, having fasted since 11:00 pm the previous evening. Height and weight were recorded, urine was collected for drug screening, and subjects were fed a standardized breakfast between 7:30–8:15 am. The imaging session began at approximately 11:00 am, with imaging of sucrose stimulation starting at ~12:00 pm (prior to which, subjects were imaged while performing one run of a monetary incentive delay task; data to be reported elsewhere).

2.2.1. Taste test

Prior to imaging, subjects tasted and rated different molar (M) concentrations of sucrose as used in similar studies (0.05, 0.10, 0.21, 0.42, 0.83 M; Kampov-Polevoy et al., 2004), prepared by dissolving table sugar in 100 ml of deionized water. Administered in three blocks, each of the five solutions was presented once per block in a randomized fashion. Subjects sampled 15 ml of each solution, "swished" for 5 s in the mouth, and spit without swallowing. Subjects rated the intensity of

Table 1
Sample demographics.

	Family history positive						Family history negative						Statistics		
	Men (n = 17)			Women (n = 20)			Men (n = 15)			Women (n = 22)			FHA	Sex	FHA × Sex
	Mean ± (SD)	Range	n (%)	Mean ± (SD)	Range	n (%)	Mean ± (SD)	Range	n (%)	Mean ± (SD)	Range	n (%)	<i>F</i> _{1,70} (p)	<i>F</i> _{1,70} (p)	<i>F</i> _{1,70} (p)
Age	23.0 (1.58)	21–26	–	23.7 (0.39)	21–26	–	22.5 (0.38)	21–26	–	21.9 (0.23)	21–24	–	11.30 (0.001)*	0.04 (0.838)	3.30 (0.073)
Caucasian	–	–	17 (100%)	–	–	15 (75%)	–	–	11 (73%)	–	–	21 (95%)	0.52 (0.472)	0.01 (0.929)	6.39 (0.014)
Education	15.1 (1.60)	12–18	–	15.2 (0.31)	12–18	–	15.4 (0.35)	12–18	–	15.2 (0.21)	14–18	–	0.26 (0.609)	0.02 (0.903)	0.33 (0.569)
AUD relatives	3.2 (1.89)	1–7	–	2.9 (0.39)	1–7	–	0.0 (0.00)	0–0	–	0.0 (0.00)	0–0	–	106.32 (0.000)*	0.23 (0.636)	0.23 (0.636)
Drinks per week	15.3 (Q1 10.4; Q3 21.0)	0.0–54.4	–	8.7 (Q1 2.8; Q3 12.2)	0.4–23.8	–	6.9 (Q1 2.6; Q3 9.4)	1.2–21.8	–	8.0 (Q1 5.2; Q3 10.8)	0.4–25.0	–	5.67 (0.020)*	2.15 (0.147)	4.22 (0.044)*
Normalized by total body water (g/L)	4.5 (Q1 2.8; Q3 5.6)	–	–	3.1 (Q1 1.0; Q3 4.9)	–	–	1.8 (Q1 0.6; Q3 2.4)	–	–	3.0 (Q1 2.0; Q3 3.8)	–	–	4.06 (0.048)*	0.01 (0.926)	3.78 (0.056)
Drinks per drinking day	4.8 (Q1 2.8; Q3 5.5)	0.0–12.6	–	3.7 (Q1 1.9; Q3 4.6)	1.0–9.2	–	3.6 (Q1 1.8; Q3 4.6)	1.3–8.0	–	4.3 (Q1 2.1; Q3 6.6)	1.0–10.7	–	0.20 (0.626)	0.09 (0.769)	2.34 (0.130)
Normalized by total body water (g/L)	1.3 (Q1 0.8; Q3 1.4)	–	–	1.3 (Q1 0.7; Q3 1.7)	–	–	1.0 (Q1 0.4; Q3 1.2)	–	–	1.6 (Q1 0.8; Q3 2.5)	–	–	0.00 (0.970)	2.85 (0.096)	3.08 (0.084)
AUDIT	10.5 (1.21)	2–20	–	9.2 (0.95)	3–16	–	7.4 (1.38)	4–23	–	8.1 (0.80)	3–20	–	3.96 (0.050)*	0.09 (0.765)	0.90 (0.346)

The italicized numbers and text are to highlight the effect of adjusting for total body water on Drinks per Week and Drinks per Drinking Day.

* The asterisks denote $p < 0.05$.

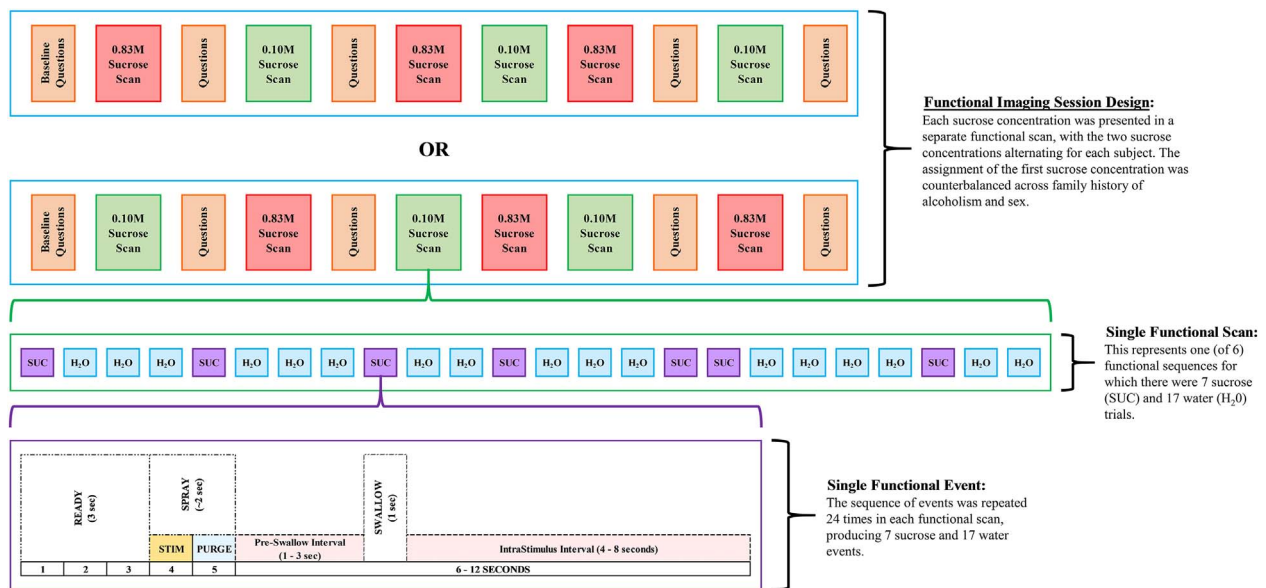


Fig. 1. Visual representation of the experimental paradigm showing two possible counterbalanced imaging session designs (top; each subject underwent only one of the two possibilities). This is followed by a representation of one of the six stimulus trial sequences presented in a single functional scan (middle, purple and blue squares). Lastly is a visual representation of a single gustatory stimulation trial within a scan (bottom). SUC = sucrose, H₂O = water.

sweetness and their subjective “liking”. After rating each sample, subjects cleansed their palates using ~10 ml of deionized water.

2.2.2. Gustatory stimulus paradigm

Fig. 1 visually depicts the gustatory stimulus paradigm. During imaging, gustatory stimuli were delivered using a computer controlled, five-channel gustometer in which gear pumps deliver solutions through a spray nozzle. Each delivery lightly covered the tongue with either 0.75 ml of a sucrose solution (0.83 M or 0.10 M) or a control stimulus of water with a tasteless thickening agent (ThickenUp Clear®, Nestlé Health Sciences, Vevey, Switzerland) to approximate the viscosity of the sucrose solution. Both sucrose and water controls were followed by 0.75 ml of thickened water (which in sucrose trials, purged the nozzle of residual sucrose). Each subject underwent one imaging session in which each sucrose concentration was presented in three separate functional scanning runs, for a total of six functional scans per subject (three 0.83 M sucrose and three 0.10 M scans, done in an alternating order within individuals, with the starting concentration counterbalanced across individuals). Within each sucrose functional scan, there were 24 trials (7 sucrose, 17 water; pseudorandomized order for each sucrose concentration). This resulted in 21 sucrose and 51 water trials for each concentration. Subjects were alerted to impending spray delivery by the text “READY” as projected onto a screen at the rear of the scanner, with “SPRAY” being displayed while the solution was presented. Subjects were asked to hold the solution in their mouth until prompted to swallow by the visual command “SWALLOW” (jittered 1–3 s after sprays). To maximize taste contrast, only water controls that immediately followed a preceding water trial were used for the [Sucrose > Water] contrast, resulting in comparisons of 21 trials of each sucrose concentration and 33 water trials for each subject. Following each scan, 1.5 ml (or more as chosen by the subject) of thickened water was delivered to the subject to rinse the mouth, with the opportunity to administer further rinses as needed by subjects individually.

2.2.3. Intra-MRI assessment

Prior to the first sucrose scan, subjects rated baseline hunger, thirst, and sweet and salt craving. Following the first two and final two functional scans, subjects rated hunger, thirst, sweet and salt cravings, perceived sweetness, liking of the sucrose solution in the prior scan, and desire to increase or decrease solution sweetness. Subjects made rated

the sucrose solutions following the first and last pair of high/low concentration scans so as to bracket all sucrose functional scans, and to avoid “rating fatigue” from repeated questioning.

2.2.4. Image acquisition

Subjects were imaged on a Siemens 3 T Magnetom Prisma (Erlangen, Germany) scanner using a 64-channel head coil array. A high-resolution anatomic volume (1.05 × 1.05 × 1.2 mm³ voxels, 3D magnetization prepared rapid gradient echo; MPRAGE) was used to position functional, blood oxygenation level dependent (BOLD) contrast sensitive data acquisition (gradient echo, echo-planar imaging [EPI], 164 measurements, repetition/echo time TR/TE = 2110/29 ms, flip angle 78°, field-of-view 220 × 220 mm, matrix 80 × 80, 39 interleaved 3 mm thick slices, 2.75 × 2.75 × 3.0 mm³ voxels, GRAPPA acceleration factor 2). The total duration of functional imaging was 50–55 min, which included brief instructions, six BOLD scans, intra-MRI assessment questions, and time for post-scan water spray delivery and subjective ratings after BOLD scans. A gradient echo field mapping scan (TR = 355 ms, TE1/TE2 = 3.86/6.32 ms) with an imaging volume and voxel size identical to BOLD EPI was acquired prior to the first BOLD scan. This 59 s scan with an advanced B0 shim mode adjustment optimized the field homogeneity and facilitated the BOLD EPI volume distortion evaluation and unwarping. This procedure yielded improved localization across the brain, most notably in the ventral striatal and frontal areas. Subjects' head movement and motion-related artifacts were minimized using foam pads and real time prospective acquisition motion correction (Thesen et al., 2000), with additional steps accounting for head motion detailed in the image analysis below.

2.2.5. Image analysis

Image preprocessing included BOLD volume unwarping using topup/aplytopup (Oxford Center for Functional MRI of the Brain Software Library; FSL, Smith et al., 2004), with slice-time acquisition correction, rigid-body realignment, and co-registration implemented in SPM8 (Wellcome Department of Imaging Neuroscience, University College, London, UK). Each subject's MPRAGE image was segmented with SPM8 and parameters from this nonlinear transformation were used to convert the subject's structural MRI and realigned, co-registered BOLD volumes into Montreal Neurological Institute (MNI) stereotactic space. The resulting volumes were interpolated to 2 mm/side isotropic

voxels and smoothed by a 6 mm full-width at half-maximum isotropic Gaussian kernel.

Within-subject fixed effects of the BOLD response to stimulus trials were estimated using SPM's canonical hemodynamic response function with time and dispersion derivatives. Sucrose and water trial conditions were modeled to an onset coinciding with gustometer pump activation and durations of 3 s. Swallowing was a condition of no interest, with onsets given by the visual cue appearance. We included, as multiple regressors, six head motion parameters from the SPM8 realignment and two FSL-derived metrics (frame displacement and DVARS from *fsl_motion_outliers*) recommended for tagging outlier BOLD volumes corrupted by large motion (Power et al., 2012). A mixed linear model found no difference in outliers within any factor. An autoregressive AR (1) model accounted for serial correlations, while a high-pass filter was set (1/128 Hz) to remove low-frequency noise.

2.2.6. Statistical analysis

The contrasts of [0.83 M Sucrose > Water] and [0.10 M Sucrose > Water] were estimated across all three scans of each concentration and entered into an SPM8 group random effects factorial model, Family History (FHP, FHN) × Sex (Men, Women) × Sucrose Concentration (high, low), permitting secondary analyses of any effects from sex. We also examined an SPM factorial model that included drinks/week as normalized by total body water to account for differences in body size in sex, and thus alcohol exposure (Stangl et al., 2017). In addition, the covariates of both drinks/week and drinks/drinking day (normalized by total body water) were tested for any associations with BOLD responses to determine if the preliminary effects we previously identified (Kareken et al., 2013) could be replicated. For ease of interpretation, however, we also present drinking data that are unadjusted by total body water (see Table 1).

To identify only those gustatory areas present in the current data set, we made statistical inferences for the main effect of sucrose (collapsed across Family History, Sex, and Concentration) at the voxel-wise height threshold $p_{FWE} < 0.05$, correcting for family-wise error (FWE) from multiple comparisons across the whole brain volume. This was the only contrast assessed across the whole brain volume, and solely to demonstrate that the paradigm activated the gustatory system overall (positive control). To test for effects related to family history, we created a mask from regions previously defined by work published elsewhere (*i.e.*, the current data were not used to generate the mask). This 9792 mm³ (1224 voxels) conjoint binary mask (Fig. S1) used for family wise error correction comprised of *a priori* hypothesized bilateral ROIs covering: (a) gustatory regions of “area-G” (insula/parietal junction) and peri-Rolandic parietal areas identified by Ogawa et al. (2005), (b) amygdala as identified by the MarsBar utility (AAL Atlas; Tzourio-Mazoyer et al., 2002), (c) posterior orbitofrontal areas identified by the Kringselbach and Rolls (2004) meta-analysis as responding to primary reinforcers, and (d) previously described ventral striatal regions (Mawlawi et al., 2001). All subsequent analyses of BOLD response (*i.e.*, all those beyond the main effect of sucrose stimulation, described above) were conducted using this independent conjoint mask for small volume correction with a height threshold of $p_{FWE} < 0.05$. Finally, we used voxel-wise linear regression to test for associations between rated sucrose liking and brain activation.

Subject group demographic data were analyzed using Family History (2) × Sex (2) general linear models. Taste test data outside the scanner were analyzed by a Family History (2) × Sex (2) × Concentration (5) × Block (3) mixed linear model, with concentration and block being repeated measures. Additional models including drinks/week and drinks/drinking day (each corrected by total body water) covariates were also used to test for the covariate effects. Intra-MRI ratings of hunger, thirst, craving for sweet and salty tastes, and desire to change sweetness were analyzed using a Family History (FHP, FHN) × Sex (Men, Women) × Time (Baseline, First Scan, Last Scan) × Concentration (pre-exposure, 0.10 M, 0.83 M) mixed linear

model, with Time and Concentration being repeated measures. Perceived sweetness and sweet liking were analyzed with Family History (FHP, FHN) × Sex (Men, Women) × Time (First Scan, Last Scan) × Concentration (0.10 M, 0.83 M) mixed linear models. To test for associations between drinking and rated liking of the sweet solutions inside the scanner, the covariates of drinks/week and drinks/drinking day (both adjusted for total body water) were also used. When examining these covariates, and for ease of interpretation, the models were simplified by removing the Concentration factor, with two different models for each concentration (0.10 M, 0.83 M).

3. Results

3.1. Subject demographics

Table 1 depicts demographic characteristics and group differences. The family history groups were insignificantly different in education. There was a statistically significant difference in age across the family history groups, although the mean effect was small, spanning approximately one year (FHP = 23.4 ± SD = 1.7, FHN = 22.1 ± 1.3). As adjusted by total body water, drinks/drinking day was not significantly different across family history groups. There was a main effect of family history in drinks/week as adjusted by total body water (FHP = 3.7 ± 3.7, FHN = 2.5 ± 1.8), but the overall model's effects accounted for little explained variance ($R^2 = 0.09$, $p = 0.083$). Similarly, there was a family history main effect for AUDIT scores (FHP = 9.8 ± 4.6; FHN = 7.8 ± 4.4), but the overall model again explained relatively little variance ($R^2 = 0.06$, $p = 0.213$).

3.2. Pre-imaging taste ratings

3.2.1. Sweet intensity

There was a main effect of Concentration for perceived sweetness (intensity; $p < 0.001$; Fig. S2A), with the 0.83 M solution rated as most intense ($p < 0.001$). A significant main effect of Block ($p = 0.032$) reflected greater perceived intensity in the third Block compared to the second. A Block × Concentration interaction ($p < 0.001$) stemmed from perceived lower intensity in the 0.05 M Concentration, with an increase in 0.83 M following the first Block. There were no FHA or Sex main effects ($ps > 0.50$).

3.2.2. Sweet liking

There were main effects of Block ($p = 0.024$; sweet liking highest in the first Block, Fig. S2B) and Concentration ($p = 0.011$; highest liking for the 0.42 M concentration), and a Concentration × Sex interaction ($p = 0.031$; men increased liking ratings with greater concentrations, while women did not). Divided into “sweet-likers” (peak liking ratings at 0.83 M) and “sweet-dislikers” (peak liking ratings < 0.83 M) with Kampov-Polevoy et al.'s (1998) criteria, 35% of both FHP (13/37) and FHN subjects (13/37) fit criteria for “sweet-liking” ($\chi^2 = 2.34$, $p = 0.67$). The remaining FHP subjects' liking ratings peaked at concentrations of 0.42 ($n = 8$), 0.21 ($n = 4$), 0.10 ($n = 6$), and 0.05 M sucrose ($n = 5$). Non-sweet-liking FHN ratings peaked at 0.42 ($n = 7$), 0.21 ($n = 6$), 0.10 ($n = 9$), and 0.05 M sucrose ($n = 2$).

Neither drinks/week nor drinks/drinking day (both adjusted for total body water) were significantly associated with liking ($ps > 0.50$) in the extra-scanner taste test models. As the covariate of drinks/drinking day interacted with Concentration ($p < 0.001$), with a trend drinks/week × Concentration interaction ($p = 0.084$), we also examined simpler models of each of the two specific sucrose concentrations used in imaging (0.1 M, 0.83 M). Here the drinking covariates were also insignificant, and did not interact with either Family History or Sex ($ps > 0.13$) in predicting liking ratings.

3.3. Intra-MRI subjective ratings

3.3.1. Hunger

A main effect of Family History ($p = 0.015$) reflected greater hunger in FHN subjects, and a main effect of Sex ($p < 0.001$) reflected greater hunger in men. There was no main effect of Time, but hunger increased over scans ($ps \leq 0.010$ comparing the last scans of both concentrations to baseline; Fig. S3A).

3.3.2. Thirst

A main effect of Time ($p = 0.001$) came from significant decreases in thirst across all scans when compared to baseline ($ps \leq 0.001$; Fig. S3B).

3.3.3. Sweet craving

A main effect of Time ($p = 0.029$) stemmed from significant declines in the last scans compared to baseline and prior scans ($ps \leq 0.029$). A main effect of Sex ($p = 0.017$) reflected greater sweet craving in men.

3.3.4. Salt craving

A main effect of Family History ($p = 0.004$) was from greater salt craving in FHN subjects, but in the context of a main effect of Sex ($p = 0.002$), and a Sex \times Family History interaction ($p = 0.009$) due to greater salt craving in FHN men.

3.3.5. Solution sweetness

As expected, a main effect of Concentration reflected higher sweet ratings for the 0.83 M concentration ($p < 0.001$; Fig. S4A).

3.3.6. Sweet liking

A main effect of Sex ($p = 0.002$), and a Family History \times Sex interaction, showed FHP men to report the greatest liking ($p = 0.001$; Fig. S4B). A main effect of Time ($p = 0.042$) reflected a significant reduction in liking from the first scan to the last.

When used as covariates, neither drinks/week nor drinks/drinking day (both adjusted for total body water) were significant factors when examining in-scanner sweet liking ratings for either of the sucrose concentrations ($ps > 0.24$).

3.3.7. Desire to change

A main effect of Concentration ($p < 0.001$) reflected a greater desire to increase the sweetness of the 0.10 M solution (Fig. S4C). A main effect of Sex ($p < 0.001$) was from men wishing to increase sweetness more than women.

3.4. BOLD responses

To assure paradigm validity, we first analyzed the main effect of BOLD activation collapsed across Family History, Sex, and Concentration (main effect of sucrose [Sucrose > Water]; Fig. 2, Table 2) as a positive control. As anticipated, the [Sucrose > Water]

Table 2

BOLD activation collapsed across sucrose concentration, group, and sex.

Region	Cluster size	Peak Z	MNI coordinates (mm)		
			x	y	z
L posterior insula (area G)	734	> 8.00	-36	-6	6
L ventral insula		> 8.00	-36	4	-12
L anterior insula		7.57	-30	16	4
R posterior insula (area G)	738	> 8.00	38	-4	10
R ventral insula		> 8.00	38	6	-12
R anterior insula		7.55	38	18	-2
R orbitofrontal (medial orbital gyrus)	125	> 8.00	22	32	-18
L postcentral gyrus	595	> 8.00	-60	-18	26
R postcentral gyrus	539	7.77	60	-12	28
R precentral gyrus		5.07	60	6	28
L orbitofrontal (medial/posterior orbital gyrus)	89	7.26	-24	36	-16
R middle frontal gyrus	211	6.28	40	42	8
R middle frontal gyrus		5.86	48	48	8
R dorsal amygdala	18	5.68	20	-2	-12
L supramarginal gyrus	45	5.25	-62	-54	34
L supramarginal gyrus		4.88	-60	-52	44
L middle frontal gyrus	15	5.12	-42	42	10
R ventral striatum	5	5.04	12	8	-2
L ventral striatum	1	4.90	-12	8	-2
L dorsal amygdala	4	4.84	-22	-6	-12

($n = 74$) BOLD activation to sucrose as compared to water collapsed across family history, sex, and concentration. MNI = Montreal Neurological Institute Coordinates in mm. Cluster sizes reflect all voxels at $p_{FWE} < 0.05$, family wise error (FWE) adjusted for whole brain multiple comparisons (t threshold = 4.97).

contrast showed that BOLD responses occurred in gustatory cortex, including “area-G” and the Rolandic operculum (*left* [-36, -6, 6]; *right* [38, -4, 10]). Also present, were BOLD responses within multiple limbic and reward areas including bilateral clusters in the ventral insula (*left* [-36, 4, -12]; *right* [38, 6, -12]), extending into the bilateral amygdala and ventral striatum. The bilateral orbitofrontal cortex (OFC) was also activated (*left* [-24, 36, -16]; *right* [22, 32, -18]); all peaks reported in text, $p_{FWE} < 0.001$ after adjusting for multiple comparisons across the whole brain).

We next confirmed the anticipated “dose effects” using a [(0.83 M > Water) > (0.10 M > Water)] contrast, which when collapsed across Family History and Sex, resulted in greater activation within primary (area-G *left* [-36, -6, 6], *right* [36, -6, 16]) and secondary gustatory areas (OFC *left* [-22, 34, -16], *right* [22, 32, -18]; amygdala *left* [-24, -4, -16], *right* [26, -6, -14]), as well as the ventral striatum *right* [8, 10, -4]) (Fig. 3 and Table 3; all peak effects, $p_{FWE} < 0.05$ after adjusting for multiple comparisons in the *a priori* conjoint binary mask).

Having assessed the “dose effect” irrespective of Family History or Sex, we tested for the roles of Family History and Sex on BOLD response. We began by examining Family History in the highest concentration of sucrose [FHP, (0.83 M > Water)] and [FHN, (0.83 M > Water)] (Fig. 4A & B, Table 3). A concentration of 0.83 M

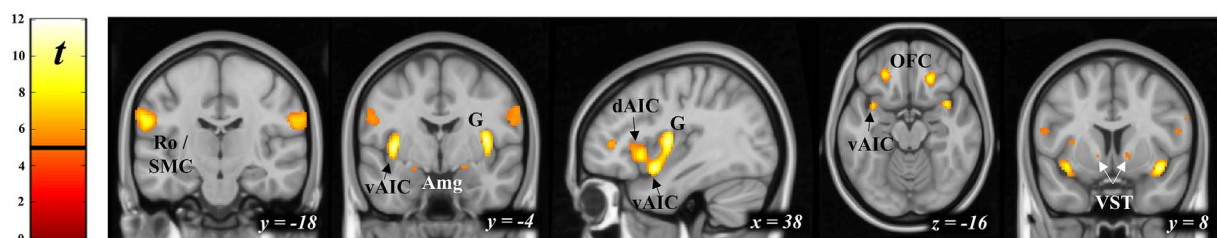


Fig. 2. [Sucrose > water] effect collapsed across Family History of Alcoholism, Sex, and Sucrose Concentration ($n = 74$). Robust activation is present in the bilateral gustatory areas of the rolandic (fronto-parietal) operculum (Ro)/Sensorimotor cortex (SMC), dorsal (“area G”) insula/fronto-parietal operculum, as well as ventral and dorsal anterior insula cortex (vAIC, dAIC). The secondary (association) gustatory areas include the amygdala (Amg), orbitofrontal cortex (OFC), and the ventral striatum (VST). Display threshold $p_{FWE} < 0.05$, $k > 0$; family wise error (FWE)-corrected for whole brain multiple comparisons. The color-bar scale indicates t statistic values with the black line denoting the display threshold.

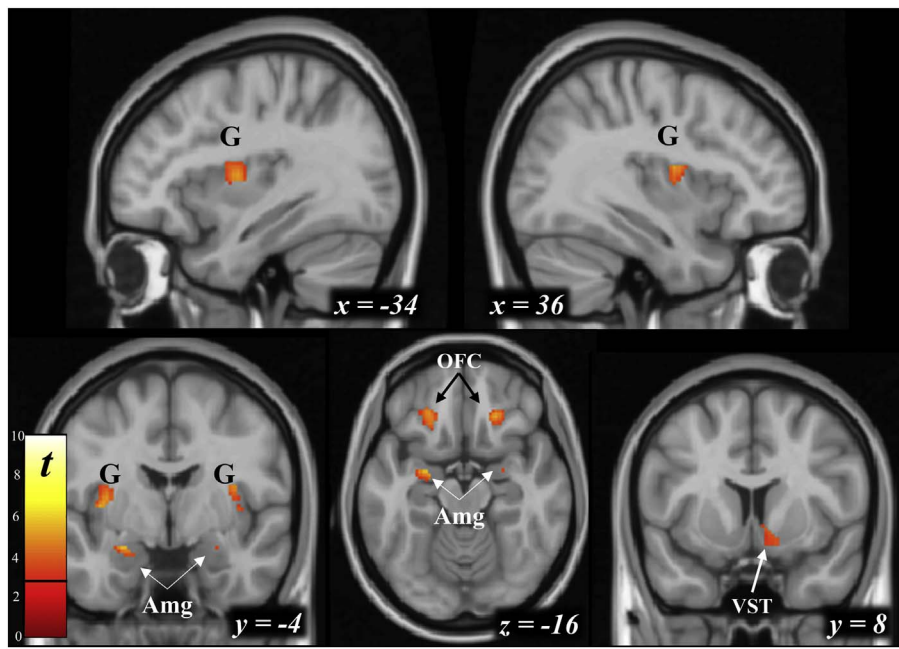


Fig. 3. Regions activating more to higher than lower sucrose concentration (e.g., [(0.83 M > water) > (0.10 M > water)]) collapsing across Family History of Alcoholism and Sex ($n = 74$). Robust activation is present in the bilateral gustatory areas of the dorsal (“area G”) insula/frontal operculum, and the secondary (association) gustatory areas including the amygdala (Amg), orbito-frontal cortex (OFC), and the ventral striatum (VST). Display threshold $p < 0.001$, $k > 0$ constrained by the conjoint mask for illustrative purposes; all peaks shown surpass $p_{FWE} < 0.05$ (see Table 3) corrected for the conjoint *a priori* ROI mask. Color-bar scale indicates t statistic values for panels with the solid bar denoting $p = 0.001$.

Table 3
BOLD Activation by sucrose concentration and group.

Region	Cluster size	Peak Z	MNI coordinates (mm)		
			x	y	z
(0.83 M > water) > (0.10 M > water) ($n = 74$)					
L posterior insula (area G)	66	5.66	-38	-6	6
R orbitofrontal (medial orbital gyrus)	87	5.33	22	32	-18
L amygdala	22	5.16	-24	-4	-16
R posterior insula (area G)	28	4.74	36	-6	16
L orbitofrontal (medial orbital gyrus)	85	4.62	-22	34	-16
R ventral striatum	7	4.08	8	10	-4
R ventral striatum		3.67	14	8	-10
R amygdala/hippocampus	1	3.82	26	-6	-14
R ventral striatum	1	3.72	8	14	-4
R posterior insula (area G)	1	3.58	38	-4	4
FHP, 0.83 M > water ($n = 37$)					
L posterior insula (area G)	132	> 8.00	-36	-8	8
R posterior insula (area G)	100	7.13	36	-4	12
R posterior insula (area G)		6.20	38	-4	4
R orbitofrontal (medial orbital gyrus)	129	6.65	22	32	-18
L orbitofrontal (medial/posterior orbital gyrus)	122	6.17	-24	36	-16
L dorsal amygdala	8	4.50	-24	-4	-16
FHN, 0.83 M > water ($n = 37$)					
L posterior insula (area G)	110	> 8.00	-38	-6	6
R orbitofrontal (medial orbital gyrus)	98	7.17	20	32	-18
R posterior insula (area G)	82	6.50	38	-6	8
L orbitofrontal (medial/posterior orbital gyrus)	72	5.75	-24	36	-16
L dorsal amygdala	5	4.36	-26	-6	-14
R ventral striatum	3	3.77	8	8	-4
FHP, 0.10 M > water ($n = 37$)					
R posterior insula (area G)	72	6.47	38	-6	10
L posterior insula (area G)	55	5.70	-36	-8	10
R orbitofrontal (medial orbital gyrus)	18	4.09	22	32	-18
L orbitofrontal (medial/posterior orbital gyrus)	1	3.69	-24	38	-16
FHN, 0.10 M > water ($n = 37$)					
No suprathreshold voxels					
FHP > FHP, 0.10 M ($n = 74$)					
R amygdala	6	3.82	26	-2	-24
L amygdala	3	3.70	-22	-6	-26

MNI = Montreal Neurological Institute coordinates in mm. Cluster sizes reflect all voxels at $p_{FWE} < 0.05$ (t threshold = 3.66), adjusted for the *a priori* conjoint binary mask comprised of bilateral Insula, Amygdala, VST, and OFC search regions (9792 mm³).

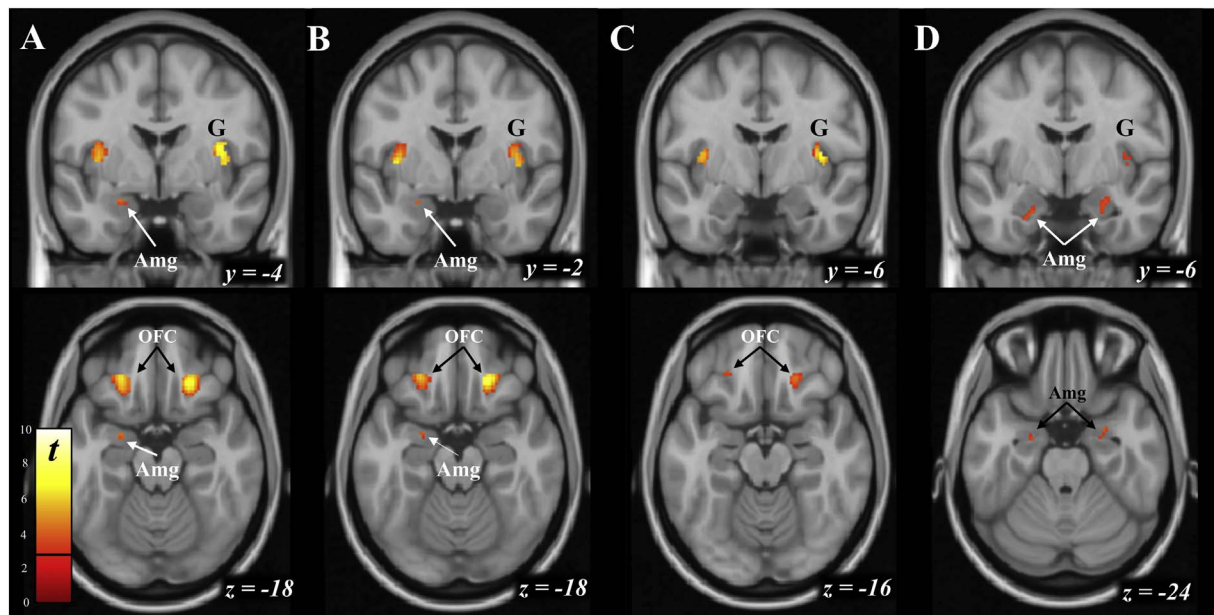


Fig. 4. Increased BOLD responses of the primary gustatory cortex in the dorsal insula/frontal operculum (“area G”), as well as, the secondary (association) gustatory areas within the orbital frontal cortex (OFC) and amygdala (Amg) for: (A) [FHP; 0.83 M > Water], (B) [FHN; 0.83 M > Water], (C) [FHP; 0.10 M > Water], (D) [FHP > FHN, 0.10 M > Water]. Display threshold $p < 0.001$, $k > 0$, constrained by the conjoint mask for illustrative purposes. Except for area G in panel D (trend $p_{FWE} < 0.097$), all peaks shown surpass $p_{FWE} < 0.05$ corrected for the conjoint *a priori* ROI mask (see Table 3). Color-bar scale indicates t statistic values for panels A–D with the solid bar denoting $p = 0.001$.

in FHP subjects resulted in significant ($p_{FWE} < 0.05$) activation within primary (area-G left $[-36, -8, 8]$, right $[36, -4, 12]$) and secondary gustatory areas (OFC left $[-24, 36, -16]$, right $[22, 32, -18]$; amygdala left $[-24, -4, -16]$) as adjusted by the *a priori* conjoint binary mask. The results within FHN subjects were very similar, with significant ($p_{FWE} < 0.05$) activation within primary (area-G left $[-38, -6, 6]$, right $[38, -6, 8]$) and secondary gustatory areas (OFC left $[-24, 36, -16]$, right $[20, 32, -18]$; amygdala left $[-26, -6, -14]$) and the ventral striatum right $[8, 8, -4]$, as adjusted by the *a priori* conjoint binary mask. As a result, there were no statistically significant differences between the family history groups from 0.83 M sucrose stimulation.

As the 0.83 M sucrose compared to water showed no differential effects in BOLD activation between FHP and FHN subjects, we next evaluated the low 0.10 M concentration of sucrose (compared to water) across Family History (Fig. 4C, Table 3). Unlike the 0.83 M sucrose concentration, the 0.10 M concentration showed family history differences in BOLD activation, with FHP showing significantly greater BOLD responses than FHN ($p_{FWE} < 0.05$, adjusted for the *a priori* conjoint binary mask) in the bilateral amygdala (right $[26, -2, -24]$; left $[-22, -6, -26]$; Fig. 4D, Table 3). There was a trend for greater FHP gustatory cortex (right insula) activation ($[38, -8, 8]$, peak $p_{FWE} = 0.097$). No regions showed greater activation to 0.10 M sucrose in FHN when compared to activation in FHP.

3.4.1. Sex effects

There were no effects of sex on the BOLD response to either concentration of sucrose. Sex did not interact with family history when analyzing BOLD responses to the 0.83 M sucrose concentration. However, sex did interact with family history when analyzing BOLD responses to the low 0.10 sucrose concentration (FHP > FHN, females > males), with the greatest responses in FHP females in the right amygdala ($[30, -2, -26]$, 10 voxels, $p_{FWE} < 0.05$ constrained by the *a priori* conjoint binary mask). However, this effect was driven principally by activation in FHP women, with deactivation present in the other groups (FHP men, all FHN subjects).

3.4.2. Drinking effects

As sweet preference has been related to drinking in some prior work, and as the family history groups differed in weekly drinking, we evaluated weekly drinking effects on the BOLD responses. When using drinks/week (adjusted by total body water) as a covariate in the voxel-wise SPM models, there was no difference in the outcome in the 0.83 M sucrose concentration. For the 0.10 M concentration, the left peak amygdala response difference between the family history groups became a trend-level effect ($p_{FWE} = 0.093$), but the right-sided effect remained (Supplementary Table 1). The trend-level effect in gustatory insula became not significant ($p_{FWE} = 0.13$). Neither drinking covariate (*i.e.*, drinks/week, drinks/drinking day, each normalized by total body water) was itself associated with any BOLD response in either the 0.83 M or 0.01 M concentrations.

3.4.3. Effects of sucrose liking ratings

As assessed in a voxel-wise correlation model, sweet liking ratings and the BOLD responses to either sucrose concentration were not related within our *a priori* mask, with the exception of a trend-level inverse association ($p_{FWE} = 0.065$, peak effect) for the 0.83 M concentration at the lateral edge of our right orbital ROI.

4. Discussion

Consistent with our earlier study (Kareken et al., 2013) and others (Dalenberg et al., 2015; Rudenga et al., 2010; Small et al., 1997; Stice et al., 2013), oral sucrose administration evoked robust primary gustatory BOLD activation spanning “area-G”, peri-Rolandic (fronto-parietal) opercular cortex, and ventral and anterior dorsal insula. The orofacial region of sensory-motor cortex was also evident. High (0.83 M) concentration sucrose alone evoked activation in associative gustatory regions, including the bilateral orbitofrontal cortices, which is thought to encode the reward valence of primary/ingested reinforcers (Kringelbach and Rolls, 2004). The ventral striatum, known for its role in incentive salience (Berridge, 2007; Berridge, 2012) was activated, as was the amygdala, which is involved in stimulus intensity encoding (Anderson et al., 2003; Small et al., 2003). Most importantly, the amygdala response to low (0.10 M) concentration sucrose was greater

in those with a family history of alcoholism.

As several studies have suggested that familial alcoholism is associated with a preference for strong (≥ 0.83 M) sucrose concentrations (Kampov-Polevoy et al., 2003a; Kampov-Polevoy et al., 2001; Kampov-Polevoy et al., 2003b; Lange et al., 2010; Wronski et al., 2007; but also see the negative studies noted in the introduction and below), we originally hypothesized that the brain response to sucrose would vary most according to familial alcoholism at the 0.83 M concentration of sucrose (but also see the negative studies of Kranzler et al., 2001; Scinska et al., 2001; Tremblay et al., 2009). However, it was at the low, 0.10 M, concentration of sucrose at which FHP subjects had significantly greater activation than FHN subjects in the amygdala (with a trend at the conservative FWE threshold in the insula taste area; “area-G”), to which gustatory cortex projects (see Rolls, 2016 for review).

The amygdala is strongly implicated in addiction, as it is known to encode stimulus intensity, irrespective of valence (Morrison and Salzman, 2010), particularly in chemical senses (Anderson et al., 2003; Small et al., 2003). Given the amygdala's role in coding intensity, our findings suggest that one endophenotypic form of alcoholism risk may be less specific to sweet tastes, *per se*, and more particular to an altered limbic sensitivity to a reinforcing stimulus. This is echoed in a series of studies in which fearful faces produced blunted amygdala activation following exposure to alcohol (Gilman et al., 2008; Gowin et al., 2016). Glahn et al. (2007) found lower amygdala activation to fearful (*i.e.*, non-reinforcing) faces in FHP subjects compared to FHN individuals, suggesting a lower response to intense environmental stimuli within the limbic system of those with a family history of alcoholism. While this is in opposition to our findings of increased limbic sensitivity (to an endogenously reinforcing stimulus), it does suggest that the amygdala's response to environmental stimuli is affected in FHP individuals.

The posterior/dorsal aspects of the insula primary house gustatory cortex. More broadly, the insula is also integral to the salience network in its more rostral extent, facilitating executive systems by triggering and switching between the central executive and default mode networks (Menon and Uddin, 2010). This is accomplished by interplay with the thalamus, which integrates sensory input before being referred to cortical, subcortical, and other limbic zones (Craig, 2002; Rolls, 2016). In addition, multiple studies observe insula activation to cue-induced drug craving (for review see, Naqvi and Bechara, 2009), including activation to alcohol cues in alcohol dependent individuals (*e.g.*, Myrick et al., 2004). More recently, greater inhibition-related insula activity was observed in FHP men performing a go/no-go task (DeVito et al., 2013). While different in task and modality (alcohol cue, non-alcoholic gustatory response, motor inhibition), this collected pattern of differences in insula reactivity as a function of familial alcoholism might suggest an endophenotypic risk marker in insular taste cortex, the sensory alerting system, or potentially both. This was the weakest imaging finding, however, with family history effects observed only at trend level with corrected statistics.

“Sweet-liking” (sucrose liking ratings peak at 0.83 M sucrose) has been posited to be associated with alcohol use disorders or familial alcoholism (Kampov-Polevoy et al., 2014; Kampov-Polevoy et al., 2004; Kampov-Polevoy et al., 1998; Kampov-Polevoy et al., 2003a; Kampov-Polevoy et al., 2001). We did not replicate these categorical findings, as “sweet-likers” were evenly distributed across men, women, and family history of alcoholism. Sweet liking ratings were also unrelated to self-reported drinking. However, subject ratings of sweet liking within the scanner were consistent with Kampov-Polevoy's findings, as FHP men expressed the greatest sucrose liking as compared to other subjects. Other studies have, however, also failed to show a positive association between sweet-liking and a family or personal history of alcohol use disorder (Bogucka-Bonikowska et al., 2001; Kranzler et al., 2001; Tremblay et al., 2009). Kampov-Polevoy et al. (2004, 2014) have nevertheless suggested that a combination of sweet-liking and high novelty seeking is most associated with alcohol use disorders, which neither we nor other negative studies analyzed. Of note, sweet liking

ratings were not significantly related to BOLD responses to either the high- or low-concentration sucrose. By contrast, we did note a small trend-level *negative* association between liking ratings and the BOLD effect in the 0.83 M concentration sucrose scans in the lateral aspect of the right orbital ROI (with the majority of the effect lying laterally outside the ROI). Such a negative association would, however, be consistent with the Kringelbach and Rolls (2004) meta-analysis indicating that lateral OFC is more sensitive to punishers, as would be the case with excessive sweetness.

There were differences in our family history groups in weekly drinking (but not drinks per occasion). When drinks/week was used as a covariate, the family history effect in the left amygdala became insignificant, although a small response remained in the right amygdala even when accounting for weekly drinking. The trend-level effect in gustatory insula became even more insignificant. This does indicate that drinking may contribute somewhat to the family history effect. Nevertheless, a true disentangling of the effects of a family history of alcoholism and drinking is likely complex, as epidemiological evidence indicates that familial alcoholism is associated with greater drinking in the population at large (Gearhardt and Corbin, 2009). This epidemiological observation also corresponds with long-known findings that familial alcoholism may also be associated with an innate tolerance to alcohol's subjective adverse effects (Quinn and Fromme, 2011; Schuckit, 1980). Thus, both drinking levels and familial alcoholism likely travel together in practice and contribute jointly, such that a covariate adjustment might not best represent the associations. A larger sample is likely needed to form subgroups of family history positive individuals that differ in drinking. This said, neither of the drinking covariates were themselves significantly associated with BOLD activation to either sucrose concentration, which does not replicate our prior observation in a much smaller sample of a positive association of drinking and lateral orbital activation to 0.83 M sucrose (Kareken et al., 2013). However, self-reported drinks/week is accompanied by a degree of error, and it is known that covariate errors attenuate the true statistical association (see Carroll et al., 2006).

Finally, some of our imaging findings hint at possible sex differences, as the right amygdala response difference to low concentration sucrose stimulation in family alcoholism was greatest in FHP females. Previous work suggests that women have a lower detection threshold for sweet tastes, and a lower, narrower band of sweet preference (da Silva et al., 2014; Laeng et al., 1993). In our data, women's liking ratings did not increase monotonically as a function of concentration, as did that of men. Subjective taste ratings did not clearly correspond with drinking or FHA in the manner previously suggested by at least some studies (Kampov-Polevoy et al., 2003a; Kampov-Polevoy et al., 2001; Kampov-Polevoy et al., 2003b; Lange et al., 2010; Wronski et al., 2007), with our data being more in line with the prior negative findings (Kranzler et al., 2001; Scinska et al., 2001; Tremblay et al., 2009). This said, in-scanner sweet liking ratings (where stimulation was more sustained) were higher in FHP men across both solutions. Collectively, the data suggest that subjective hedonic responses (most different in FHP men) and limbic brain responses (most different in FHP women) may be providing different kinds of information.

There are limitations to this study. First, the sample is not evenly divided between men and women. Though unlikely given the still large number of men, the increased differential activation observed only in FHP women could result from this imbalance. Moreover, the family history by sex interaction in the amygdala seems to have been most driven by activation in FHP women and deactivation in the other groups. As this current sample represents findings from the first half of this ongoing study, we hope to clarify these aspects, as well as replicate the current findings in the second half of the sample by using these results to predict the location of effects in the second half of the study. While a high concentration of sucrose might be expected to elicit greater activation in FHP subjects, the 0.83 M concentration may have led to a “ceiling effect” in the brain's response, with the gustatory,

reward, and salience response being saturated by a solution approximately 2.5 times the sweetness of Coca-Cola Classic®. This may explain why we observed activation that varied by familial history only at the low concentration. Future work should then consider more intermediate concentrations. Our chosen sample of individuals who do not meet the criteria of an alcohol use disorder may also be considered a limitation, as social drinkers with a family history of alcoholism may possess protective factors that shield them from an alcohol use disorder. It is possible that, if such protective factors exist, they may also alter sweet preference in these individuals. However, Kampov-Polevoy has demonstrated that this increased sweet preference can be shown in non-alcoholics with a familial history of alcoholism (e.g., Kampov-Polevoy et al., 2004). Another potential limitation is the uneven balance of prior depression/anxiety, as well as, nicotine use as both are more prevalent in the FHP group. However, there was no behavioral evidence that prior diagnosis of depression/anxiety had any effect, and nicotine use did not significantly alter taste sensitivity as measured by the taste test procedure. Finally, a sweet taste is both inherently rewarding, but also capable of cephalic phase digestive processes and stimulating urges to eat. In that vein, this work cannot distinguish between sucrose as a pure “reward” in and of itself, and something that is provocative of ingestive urges.

5. Conclusions

In summary, this is the first study to show a brain response to oral sucrose stimulation that differs as a function of familial alcoholism. Moreover, there is some limited evidence of a sex effect, with FHP women most strongly influencing the effect at the lowest concentration of sucrose. Although we did not observe a clear association between sucrose preference and a family history of alcoholism using a taste test similar to that employed by Kampov-Polevoy et al. (1998), FHP men's liking of the sucrose solutions during fMRI was significantly greater than other subjects. Weekly drinking may account for some, but not all, of this family history effect. Taken together, these findings might suggest that the brain response to a mildly reinforcing primary reward may be an endophenotypic marker of alcoholism risk.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2017.12.019>.

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