Network organization during probabilistic learning via taste outcomes

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GRAPHICAL ABSTRACT
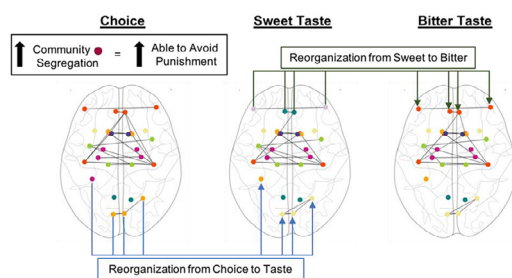
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ABSTRACT

Reinforcement learning guides food decisions, yet how the brain learns from taste in humans is not fully understood. Existing research examines reinforcement learning from taste using passive condition paradigms, but response-dependent instrumental conditioning better reflects natural eating behavior. Here, we examined brain response during a taste-motivated reinforcement learning task and how measures of task-based network structure were related to behavioral outcomes. During a functional MRI scan, 85 participants completed a probabilistic selection task with feedback via sweet taste or bitter taste. Whole brain response and functional network topology measures, including identification of communities and community segregation, were examined during choice, sweet taste, and bitter taste conditions. Relative to the bitter taste, sweet taste was associated with increased whole brain response in the hippocampus, oral somatosensory cortex, and orbitofrontal cortex. Sweet taste was also related to differential community assignment of the ventromedial prefrontal cortex and ventrolateral prefrontal cortex compared to bitter taste. During choice, increasing segregation of a community containing the amygdala, hippocampus, and right fusiform gyrus was associated with increased sensitivity to punishment on the task's posttest. Further, normal BMI was associated with differential community structure compared to overweight and obese BMI, where high BMI reflected increased connectivity of visual regions.

Together, results demonstrate that network topology of learning and memory regions during choice is related to avoiding a bitter taste, and that BMI is associated with increased connectivity of area involved in processing external stimuli. Network organization and topology provide unique insight into individual differences in brain response to instrumental conditioning via taste reinforcers.

1. Introduction

Overweight and obesity affects over two thirds of American adults [1], making it a major preventable risk factor for a number of diseases including type 2 diabetes [2–4], certain types of cancer [5,6], and cardiovascular disease [7–9]. A variety of individual, social, and environmental factors contribute to the development of overweight and obesity, but eating behavior is considered a key point of study for understanding the etiology of obesity [10]. Eating behavior is the product of repeated choice outcome pairings and the food selected provides the reinforcement. When making a choice about what to eat, information from internal states [11], food preferences [12], dietary goals [13], and the environment [14,15] are integrated in the brain, which selects the best action to perform a motivated action (e.g. satiating hunger, satisfying a craving, or following a diet). These decisions are represented by increased brain response in regions across the prefrontal and cingulate cortices [16]. Regions include the medial orbitofrontal cortex (mOFC), which encodes the value of an outcome [17], and the anterior cingulate cortex (ACC), a region that assesses the cost of actions [18]. Decision making also involves the ventromedial prefrontal cortex (vmPFC), which weighs the value of an outcome against the costs associated with the action to assign overall value to actions [19,20] and the dorsolateral prefrontal cortex (dlPFC), a region that modulates computations [20].

Once a choice is made, consuming the food selected provides initial information about the reinforcing properties of foods via the generation of flavor perceptions, varying from delicious to disgusting. Sweetness, an indicator of the potential presence of energy [21], is generally found to increase pleasantness, whereas bitterness indicates the potential presence of a toxin [22] and, at least initially, promotes dislike. Both sweet and bitter taste therefore serve as important sensory signals to promote or prevent future consummatory behavior [23]. Post-oral signals are generated following consumption and update acceptability based on beneficial or adverse ingestive consequences [16]. This process of repeated food choice, consumption, and reinforcement can be operationalized as instrumental conditioning [24]. Following the instrumental conditioning framework: individuals learn to associate a cue (food image or logo) with a given response (e.g. choosing or avoiding the food), and the subsequent reinforcement from consuming the food. This process recruits aforementioned decision-making brain regions, and integrates signal from areas involved in motivation and taste processing [16]. Neural response to taste is well characterized - palatable taste evokes response in the striatum, insula, dorsal ACC, OFC, and amygdala [25,26], while bitter taste also activate the OFC and amygdala [27,28].

Typical analyses of functional neuroimaging data provide information about how blood oxygen-level dependent (BOLD) response in the brain changes in response to a given stimulus, but does not capture how areas the brain interact in response to the stimulus. Cognition and behavior are the product of a coordinated flow of information between brain areas, and network-based approached provide important detail on the functional organization of the brain during response to a stimulus [29]. Functional connectivity is undirected, and can exists between spatially distinct regions, theoretically reflecting synchronous response. For example, functional connectivity is increased between the ventral striatum, insula, amygdala and hippocampus during reinforcement via monetary gain [30]. In response to a palatable taste reinforcer, functional connectivity of the OFC and insula is increased [31]. Network-based analyses of BOLD response apply graph-theory to functional connectivity and provide information about the architecture of brain networks, and can be applied to identify differences in the functional organization of brain response across conditions or individuals [32,33]. Regions of the brain are treated as "nodes" of a graph and the correlations between nodes (brain regions) as "edges" [34]. Metrics include the organization of brain regions into functional subnetworks, called "communities," that are theorized to perform specialized task (modularity); the density of connections of a region and its neighbors (segregation); the centrality of a region in paths between other area (hubness), and the ratio of with-community connections to out-community connections (integration) (Figure 1) [35]. During reinforcement and motor learning, the communities reorganize, such that the communities become more segregated with learning, supporting the development of specialized function within segregated subnetworks [36,37] Network organization of the basal ganglia is particularly important in this process [38]. To date, brain network organization during food reinforcement has not been tested.

The extant studies on brain response during food reinforcement primarily use passive, Pavlovian conditioning tasks, where no choice is involved. Pavlovian conditioning and instrumental conditioning via secondary reinforcers are associated with differences in BOLD response [39], so it stands to reason that brain response during taste-mediated instrumental conditioning may diverge from prior response to passive conditioning tasks. Additionally, tasks assessing brain response during instrumental conditioning primarily use secondary reinforcers such as

Characteristic	Measure	Description	Node with High Value
Segregation	Clustering Coefficient	The number of connected triangles compared to possible triangles	A
Integration	Participation Coefficient	The ratio of in-community connections to out-community connections	B
Hubness	Betweenness Centrality	The number of shortest paths between nodes that travel through that node	C

● Community 1 ● Community 2 ● Community 3 ● Community 4
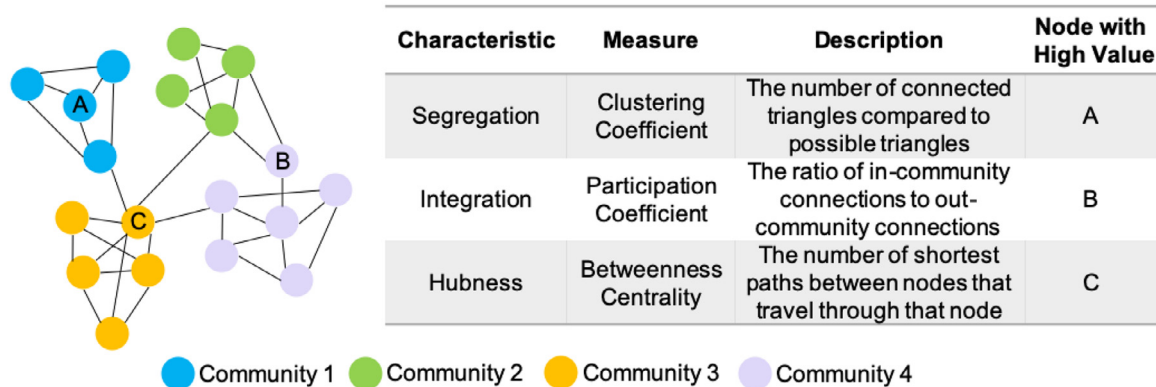
Figure 1. Graph Theory Measures of Functional Network Organization

Table 1
Reinforcer Composition and Selection

Flavor	kcal[a]	Sugar (g)[a]	Quinine (mg)[a]	Malto-dextrin (g)[a]	Selected as Reinforcer
Sweet 1	104.6	14.2	–	20.9	11 (12.9%)
Sweet 2	105.4	21.2	–	10.5	17 (20.0%)
Sweet 3	105.4	28.2	–	5.3	20 (23.5%)
Sweet 4	105.4	35.1	–	0.0	37 (43.5%)
Bitter 1	105.3	7.0	12.0	7.0	5 (5.9%)
Bitter 2	105.3	6.8	24.0	7.1	11 (12.9%)
Bitter 3	105.3	6.3	48.0	7.2	19 (22.4%
Bitter 4	105.3	5.5	72.0	7.4	50 (58.8%)

[a] Values reported for 300mL portion of each beverage

money or written feedback. A primary reinforcer, such as food, may have more saliency [40] and could contribute to different network organization and dynamics over learning [41]. Thus, to address gaps in our understanding of brain response and network structure during instrumental conditioning, this study tested brain response during completion of a response-dependent conditioning task with taste reinforcement. We adapted a canonical probabilistic learning task, which measures instrumental learning from reward and punishment [42], by using beverages as reinforcers. The primary aim of the study was to identify whole brain response and explore network organization using a priori regions of interest (ROI) based analysis during the task, specifically in the choice, sweet taste, and bitter taste conditions. We hypothesized that choice would be associated with BOLD response in the medial OFC, vmPFC, and dlPFC, that sweet taste would be associated with response in the insula, dorsal ACC, OFC, and amygdala response, and bitter taste would be associated with response in the OFC and amygdala. For network analyses, we hypothesized that choice will be associated with a fewer number of communities than reward and punishment, reflecting more synchronization across the brain during

choice. In addition to these aims, we also tested if measures of network segregation, hubness, and integration were connected to behavioral outcomes including task performance and preference ratings of the sweet and bitter beverages. We hypothesized that increased community segregation across conditions would be associated with improved task performance as measured by posttest accuracy.

2. Materials and methods

2.1. Sample

Ninety (n = 90) male and female participants were recruited from the Chapel Hill, North Carolina area to complete a cross sectional study. Eligibility criteria included: 1) age 18-28 years, 2) body mass index between (BMI) 20.0 kg/m2 and 32.0 kg/m2. Exclusion criteria were: 1) contraindications of MRI (e.g. metal implants, piercings, pregnancy), 2) current smoking, 3) self-reported current or past diagnoses of an eating disorder, 4) chronic illness or medication requirement that could affect diet, 5) diagnosis of a major psychological condition (bipolar, schizophrenia, major affective disorder), and 6) allergy or intolerance to any study foods. The Institutional Review Board of the University of North Carolina at Chapel Hill approved all methods and study participants gave written consent before the start of testing. For this analysis, three (n = 3) participants who ended scanning early and two (n = 2) participants who had < 29 trials (representing 56% of possible trials) of reward or punishment were excluded. The resulting analytic sample was n = 85 participants.

2.2. Measures

Participants completed all measures in a 2.5 hour visit at the University of North Carolina at Chapel Hill's Gillings School of Global Public Health and Biomedical Research Imaging Center (BRIC).
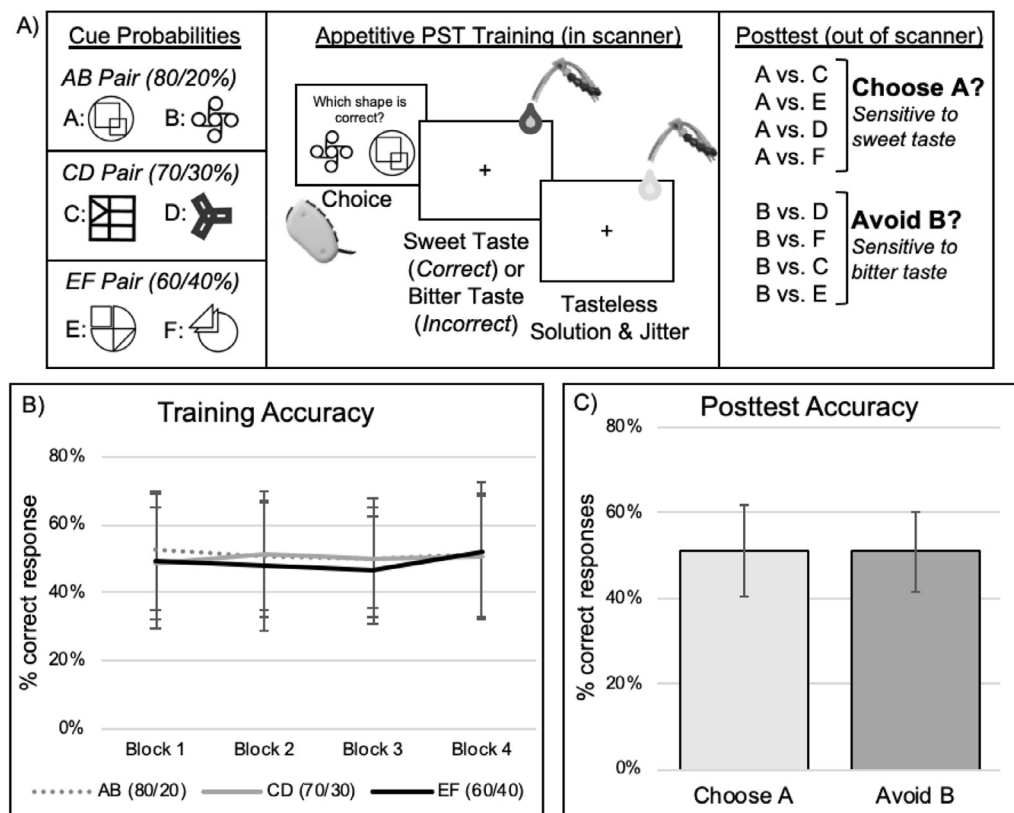

Figure 2. Appetitive PST Task and Performance

Participants were instructed to fast for four hours before the visit to standardize time since last meal. Visits took place within the hours of 7:00 and 20:00. Participants were instructed to fast for at least 4 hours before their assessment.

2.2.1. Anthropometrics & Demographics

Height (to the nearest 0.5 cm) and weight (to the nearest 0.1 kg) were measured with a wall-mounted stadiometer and a calibrated scale by trained research staff. BMI was calculated as kg/m2. Demographics including age, race, and ethnicity were assessed via self-report.

2.2.2. Beverages and Preference Assessment

Beverages used in the instrumental conditioning task as reward and punishment were selected based on participant ratings via a taste test. During the taste test, participants were instructed to taste and rate 20mL samples of 4 sweet and 4 bitter beverages. The eight beverages were made from a base of water (940mL), unsweetened Kool-Aid® Cherry powder (4.5g) and simple syrup (60 mL). Simple syrup or a quinine solution were added to the beverages to create different levels of sweetness or bitterness. The composition of the beverages can be seen in Table 1. The beverages were calorically-matched with the addition of maltodextrin, a soluble, neutral-tasting carbohydrate powder. Levels of sweetness and bitterness were selected from previous studies of taste preference [43]. Beverages were rated in pleasantness, desire to consume, sweetness, bitterness and intensity on VAS anchored at -100 and 100 (sample anchors were stated as 'most imaginable' and 'least imaginable' with 0 identified as neutral). All sweet beverages were sampled in a random order, then participants ranked the beverages from most pleasant to least pleasant, with the highest ranked beverage selected as the reward for the probabilistic selection task (see 2.2.4). The same process was then completed with the bitter beverages, and the lowest ranked beverage was selected as the punishment.

2.2.3. Neuroimaging Methods

Anatomical and functional imaging data were collected in a Siemens Prisma 3T scanner (Siemens Medical Solutions, Munich, Germany) at UNC's Biomedical Research Imaging Center (BRIC). Visual stimuli were presented with a digital projector/reverse screen display system. Tastants were delivered using programmable syringe pumps (Braintree Scientific BS-8000, Brain-Tree, MA) operated through a program written in PsychoPy [44], available at: https://github.com/niblunc/bevel_task) to ensure consistent volume, rate, and timing of taste delivery. A set of tubing attached to the scanner bed was placed into the participants' mouths and delivered the tastes. Button press response was collected via a 5-button response pad (Current Designs Pyka Response Pad, Philadelphia, PA) held in the participant's right hand. Blood-oxygen-level-dependent (BOLD) signal was collected during functional runs under the following scanning parameters: TR = 2000 ms, TE = 20ms, flip angle = 80°, with a spatial resolution of 3.0mm. Images were collected with whole-brain coverage; 32 4mm slices (interleaved acquisition) were acquired along the AC-PC transverse, oblique plane as determined by the midsagittal section. Anatomical scans were acquired with a TR/TE of 2100ms/2.4ms, flip angle of 15°, TI of 1100ms, matrix size of 256 × 256, FOV of 22cm, and slice thickness of 1mm.

2.2.4. Appetitive Probabilistic Selection Task

Participants completed a modified, taste-based version of the Probabilistic Selection Task [42], measuring response to reward and punishment (Figure 2). The task was composed of training and posttest phases. In the training phase, participants were presented with pairs of novel shapes, and asked to select the "correct" shape to receive a sweet taste. Participants were instructed that when they chose "incorrectly", they would receive a bitter taste. Feedback was probabilistic; each shape was reinforced at a prespecified probability. Three pairs were presented during the scan: 1) AB pair (A: 80% correct; B: 20% correct);

2) CD pair (C: 70% correct, D: 30% correct); 3) EF pair (E: 60% correct, F: 40% correct). Instances where participants selected the higher probability shape but received a bitter taste or where participants selected the lower probability shape but received a sweet taste were classified as "prediction errors". Pairs were presented in a random, intermixed order. Taste feedback (3mL of sweet taste or 3mL of bitter taste) was delivered over 5 seconds in the absence of any visual stimuli then followed by a 1mL rinse of a tasteless solution made to mimic the taste of saliva, delivered over 2 seconds. The next trial proceeded following a 3-7 second variable gap, during which a fixation cross was shown. In total, participants completed 104 training trials over four runs, each 6 minutes and 44 seconds in length. Following the training phase during the fMRI scan, participants completed the posttest phase of the task outside of the scanner. During the posttest, participants were presented with one shape from the AB set (A: 80% correct, B: 20% correct) paired with shapes from the other two sets and asked to select the shape that is more likely to be "correct". The proportion of trials in which the participant selects the A shape is considered their sensitivity to sweet taste, and the proportion of trials in which the participant avoids the B shape is considered their sensitivity to bitter taste.

2.3. Appetitive Probabilistic Selection Task Performance

Statistical analyses of task data were carried out using the R statistical software package (Version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria). PST task performance was calculated as the percent of correct choices, defined as choosing the shape with the higher likelihood of being correct in each pair. The percent of AB trials where A was selected, the percent of CD trials where C was selected, and the percent of EF trials where E was selected were calculated over the 4 training blocks, representing participant's training accuracy (Figure 2B). Repeated measures ANOVA was implemented using the 'lme4' package (v 1.1) to test for significant change in task performance by pair over runs, accounting for intra-individual correlation. Posttest accuracy was calculated as the percent of correct choices, defined by selecting the A shape (sensitivity to sweet taste), and avoiding the B shape (sensitivity to bitter taste). Posttest performance was correlated with brain response as a categorical regressor (See 2.7). For categorical analyses, participants were categorized as 'learners' if their posttest accuracy was above chance (50%), and as 'non-learners' if their posttest accuracy was below chance.

To test if posttest performance reflected learned preferences rather than probabilistic learning, the absolute value of the differences between sensitivity to sweet taste and sensitivity to bitter taste scores from chance accuracy (50%) was calculated to represent learned preference. Learned preference scores were correlated with brain response as a continues regressor (See Supplemental Materials).

2.4. FMRI Preprocessing

Neuroimaging data were preprocessed using the fMRIPrep pipeline [45]. In brief, DICOMS were converted to the Brain Imaging Data Structure (BIDS file structure) [46], then preprocessed using fMRIPrep. FMRIPrep preprocessing included skull stripping using Advanced Normalization Tools (ANTs); tissue segmentation using FSL's Automated Segmentation Tool (FAST); and spatial normalization to Montreal Neurological Institute (MNI) 152-Asymmetrical space using ANTs' registration option. FreeSurfer was used to reconstruct surfaces from structural images. Functional images were then motion corrected using FSL's MCFLIRT, corrected for fieldmap distortion, and spatially smoothed using a 6mm Gaussian full width half maximum isotropic kernel. In FSL, final preprocessing included adjusting for autocorrelation and highpass filtering and adjusting for nuisance regressors, including the 6 motion parameters, their derivatives, and high motion time points (>0.9).

2.4. FMRI Group-Level Main Effects Analysis

Neuroimaging analyses were primarily completed in FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl) Individual and group level analyses were carried out in FSL's FMRI Expert Analysis Tool (FEAT; [47,48]. At the individual level, within subject models assessed brain response to 1) choice via button press > baseline; 2) reward via sweet taste > rinse; and 3) punishment via bitter taste > rinse. Individual level contrasts also included reward > punishment; and punishment > reward. Motion parameters were included as nuisance regressors at the individual level.

At the group level, the analysis followed a one sample F-test model to identify whole brain response that was significantly different within the full sample. Main effect models were examined for the following contrasts: 1) choice > baseline (fixation cross); 2) sweet taste > tasteless solution; 3) bitter taste > tasteless solution; 4) sweet taste > bitter taste; and 5) bitter taste > sweet taste. Multiple comparisons were controlled for by using the threshold free cluster enhancement, nonparametric thresholding algorithm in FSL's Randomise (n permutations = 5000) resulting in a family-wise error rate corrected significance threshold of pFWE < 0.05 [49]. Localization of significant clusters were determined using Mango's MNI atlas tool.

2.5. Betaseries and Functional Connectivity

A betaseries regression analysis was used to measure condition-specific functional connectivity in the sample [50]. In each participant's preprocessed data, separate general linear models were set with a regressors modeling each event and another regressor modeling all other events of the same condition to derive condition-wise whole brain beta values for each event [51]. Conditions included: 1) choice and button press; 2) reward; 3) punishment. The resulting beta images were concatenated by condition and run, producing a timeseries of beta values, or betaseries for each condition and for each participant. Then, average signal was extracted from each participant's betaseries in 28 regions of interest (ROIs) drawn from the Big Brain 300 parcellation, a functional parcellation based on the Power atlas [52], with improved coverage of subcortical regions [53]. ROIs were selected based on regions reported as responsive to taste stimuli, taste administration, and reinforcement learning [54–58] (Table 4). The resulting betaseries arrays represented average parameter estimates in each ROI for each event in a given condition. Matrices were the same size (28 × 104) in the choice condition. Because reinforcement varied, reward and punishment matrices varied in length from 28 × 29 to 28 × 64. Betaseries correlation matrices for the 28 ROIs were extracted, resulting in 28 × 28 betaseries connectivity matrix for each condition, for each participant. For methods and results of significance testing of functional connectivity (ROI – ROI correlation), see Supplemental Materials.

2.6. Graph construction & network topology

To examine network topology during choice, reward, and punishment, betaseries correlation were used as the basis of network graphs. The 28 ROIs were treated as nodes, and correlations between ROIs were treated as graph edges. For graph analysis, only positive correlations were included, since network topology measures are not optimized for negative correlations [59]. To generate graphs, participants' correlation matrices were fed into 'networkX' package (version 2.3) [60] and 'bctpy' package (version 0.5.1, https://pypi.org/project/bctpy/), implemented in Jupyter Notebook [61], running Python 3.7.5 (Python Software Foundation).

Within each participant's graph, modularity, or the degree to which the network may be subdivided into such clearly delineated groups called communities, was calculated using the Louvain algorithm [62] 'python-louvain' package (version 0.13). Modularity was calculated on the median graph, rather than the mean graph, to account for skewness.

Then the median graph was partitioned into the identified communities, and the weighted edges between communities were calculated to examine the connectivity between communities.

Measures of network topology were also computed for each node within participant's graphs, then metrics were averaged across all nodes in the communities identified at the group level, producing average community parameters for networks associated with choice, reward, and punishment. Three parameters were calculated: (1) Weighted clustering coefficient, or the geometric average of the subgraph edge weights, was used to assess segregation via networkX's 'cluster' algorithm [63]. Higher clustering coefficient values suggest greater separation of a node from nodes outside its module. (2) Weighted betweenness centrality which measures community hubness by the fraction of all shortest paths in the network that contain a given node, and calculated using via networkX's 'betweenness_centrality' algorithm [64]. Higher betweenness centrality suggests increased participation in paths between other nodes, and higher hubness. (3) Participation coefficient, or the ratio of within-community connections compared to between-community connections, measures how integrated a node is within its community and the network. Participation coefficient was calculated using bctpy's 'participation_coef' algorithm [65]. Participation coefficients closer to 1 are indicative of greater within-community connectivity, while participation coefficients closer to 0 represent greater between community connectivity. For each participant's graph, clustering coefficient, betweenness centrality, and participation coefficient was calculated at the node level, then averaged across communities. All analyses were performed in non-thresholded, weighted graphs. To visualize modularity and nodal connectivity results, a mean graph of all conditions was created, then thresholded at the average edge strength (> 0.30) to display strongest edges.

2.7. Associations between network topology and participant characteristics

To examine differences in network structure associated with participant characteristics, we tested for group-based differences in network organization on three categorical variables: BMI, sex, and posttest performance. To examine differences in network structure between BMI groups, sample was separated into normal BMI (n = 52; BMI < 25.0 kg/m2) and overweight/obese BMI (n = 33; BMI > 25.0 kg/m2). Modularity was then calculated in the mean normal BMI graph and mean overweight/obese BMI graph. Community organization was compared between male (n = 42) and female (n = 43) participants, and participants who scored above 50% on the appetitive PST posttest (n = 45) and those who scored below 50% (n = 40). For each pair of groups, differences in community assignment were compared qualitatively and quantitatively using the normalized mutual information (NMI) score ([66], similar methods as [67]). NMI scores range from 0 to 1 with higher scores reflecting more similar community assignment between groups. To identify empirically meaningful differences in network organization, we compared observed NMI scores to a distribution of null NMI scores generated by randomly splitting individual matrices into null groups and comparing community organization. Null NMI scores were calculated over 500 permutations to generate a null distribution of NMI values for each contrast. Observed NMI values that exceeded one standard deviation of the mean of the null distribution, were considered a quantitative measure of meaningful differences in community organization.

Further, we tested for associations between community metrics (segregation, integration, and hubness) and behavioral outcomes including stimuli ratings, the level of sweetness/bitterness and posttest performance in R statistical software package (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria). Tests included Pearson's product-moment correlation for continuous measures (pleasantness and desire VAS ratings, posttest sensitivity to reward, posttest sensitivity to punishment) and one-way analysis of variance (ANOVA) for categorical measures (sweetness of reward selected and bitterness of

punishment selected) using the 'lmer' function from the 'lme4' package [68]. Significance was considered at multiple-comparisons corrected p-value threshold < 0.008.

3. Results

3.1. Participant Characteristics

Participants characteristics and performance on the instrumental conditioning task are summarized in Table 2. The sample was primarily young, normal-weight adults. The majority of participants identified as white and non-Hispanic. Just over half of the participants were female.

3.2. Appetitive Probabilistic Selection Task Performance

Out of the 104 training trials in the modified Probabilistic Selection Task, participants responded to receive reinforcement on an average of 98.1 ± 5.6 trials. About half of those trials were reinforced with the sweet taste (mean = 49.8 ± 6.0 trials), while participants also received a high number of bitter taste (mean = 48.4 ± 5.7 trials). Average accuracy did not increase over course of training (Figure 2B). On the PST posttest, participants chose shape A on 51.0 ± 11.0% of trials, representing their sensitivity to sweet taste (Table 2; Figure 2C). Participants avoided shape B on 51.0 ± 9.0% of trials, representing their sensitivity to bitter taste. The correlation between sensitivity to sweet taste and bitter taste was low (r = 0.135). Based on posttest performance, 45 participants were able to choose shape A and avoid shape B on over 50% of trials, classifying as 'learners', while 40 participants we classified as 'non-learners' as their posttest accuracy was below 50%. There were no significant correlations between posttest performance and individual factors such as BMI, age, VAS ratings of the sweet and bitter tastes, training performance or the percent of prediction error trials (correlation coefficients (r): 0.002 – 0.201; see Supplemental Materials for full results), and there were no significant differences between the 'learner' and 'non-learner' groups in the individual factors examined (p's: 0.09 – 0.81; see Supplemental Materials for full results).

3.3. Brain response during choice, sweet taste, and bitter taste

We observed robust main effects during choice via button press, sweet taste, and bitter taste. During choice via button press, BOLD response was observed across the occipital cortex and temporal lobe, insula, primary motor cortex, as well as anterior cingulate cortex, and orbitofrontal cortex (Table 3; Figure 3A). In response to sweet taste (contrasted against rinse), response was found across a number of regions including peaks in the temporal lobe and hippocampus, lateral occipital cortex, and frontal pole, in addition to response in the insula, precuneus, thalamus, left dorsolateral prefrontal cortex, amygdala, and oral somatosensory cortex (Table 3; Figure 3B). In response to bitter taste (contrasted against rinse), a similar pattern of response to reward was found, with peaks in the thalamus, oral somatosensory cortex, and anterior cingulate (Table 3; Figure 3C). When comparing whole-brain response to sweet taste contrasted against bitter taste (sweet taste > bitter taste), robust response extended into regions that traditionally respond to rewarding food stimuli, including response in the oral somatosensory cortex, precuneus, and orbitofrontal cortex (Figure 3D). Sweet taste was also associated with greater response in the hippocampus, dorsal anterior cingulate cortex, and caudate. Conversely, bitter taste contrasted against sweet taste (bitter taste > sweet taste) was related with increased response in the paracingulate gyrus (Figure 3D).

3.4. Network Organization during Choice, Sweet Taste, and Bitter Taste

Overall community organization is shown in Figure 4. During choice, ROIs organized into seven communities (Table 4), including a

learning and memory community (1: amygdala, hippocampus, and fusiform gyrus), a motivation, motor response and behavioral control community (2: dorsal striatum, pre/postcentral gyrus, ventromedial PFC, and ventrolateral PFC) and a visual response and valuation community (3: medial OFC, intracalcarine cortex, fusiform gyrus). During sweet taste and bitter taste, ROIs organized into eight and seven communities respectively (Table 4). Overall, community assignment during bitter taste was similar to sweet taste and choice. However, the ventromedial PFC and ventrolateral PFC were assigned to distinct communities during sweet taste, while during bitter taste, the ROIs were assigned to community 2 (Table 4, Figure 4).

3.5. Association of Network Topology with Task Performance, BMI and Sex

Differences in community organization between BMI groups were observed (Figure 5A). During response to sweet taste, ROIs in the bilateral intracalcarine cortex and right fusiform gyrus were organized into a single community in participants with normal BMI (n = 52). Among participants with an overweight or obese BMI (n = 33), the ROIs were assigned to a larger community including the left fusiform gyrus and bilateral medial OFC. To test if the observed differences were quantitatively meaningful, we calculated a normalized mutual information (NMI) score for the BMI-groups' community assignment, then compared it to a distribution of null scores generated from permutation testing with random group assignment. The observed NMI describing the differences between BMI groups in community organization during sweet taste (0.669) was greater than 1 SD lower than null NMI distribution mean (mean ± SD: 0.791 ± 0.102; Figure 5B), supporting that the observed differences are not due to random variation in assignment.

Segregation of community 1 during choice (amygdala, dorsal striatum, fusiform gyrus) was significantly associated with sensitivity to punishment as assessed on the probabilistic selection task posttest (r = 0.289, t = 2.73, df = 82, p = 0.0077; Figure 5C). Measures of community segregation, integration, or hubness during sweet taste and bitter taste relate to posttest performance (%sensitivity to punishment or %sensitivity to reward) or reinforcer characteristics (ratings of pleasantness and desire to consume, sugar content, or quinine added) (p's: 0.016 – 0.99). Differences in community assignment were observed between posttest accuracy groups as well as between male and female

Table 2
Participant Characteristics and Task Performance (n = 85)

	Mean ± SD	Min - Max
Age (years)	21.5 ± 2.4	18 - 28
BMI (kg/m2)	24.7 ± 3.2	19.6 - 33.1
Pre-scan Hunger	16.1 ± 46.1	-100 - 80
Sweet Taste Pleasantness	38.7 ± 19.1	-32 - 100
Bitter Taste Pleasantness	-45.5 ± 25.8	-96 - 19
Sex	Count	Percent
Male	42	49.4%
Female	43	50.6%
Race		
Black or African American	4	4.7%
Asian or Pacific Islander	19	22.4%
White	51	60.0%
Middle Eastern	2	2.4%
More than one race	5	5.9%
Other or chose not to report	4	4.7%
Ethnicity		
Hispanic	10	11.8%
Non-Hispanic	75	88.2%
PST Performance	Mean ± SD	Min - Max
Training Rewards (n)	49.8 ± 6.0	29 - 63
Training Punishments (n)	48.4 ± 5.7	31 - 64
Prediction Error Trials (%)	27.8 ± 4.4	18.4 – 38.2
Posttest Sensitivity to Sweet	51% ± 10.6%	29.2% - 75.0%
Posttest Sensitivity to Bitter	50.8% ± 9.3%	29.4% - 83.3%

Table 3
Significant BOLD Response to Cues and Reinforcement

Contrast & Regions	k[a]	Z	pFWE1	X[b]	Y	Z
Choice (AB/CD/EF Stimuli) > Rest						
Occipital cortex and temporal lobe (bilateral)	11594	11.3	<0.001	33	-48	-18
Precentral gyrus (bilateral)	1268	9.3	<0.001	0	15	48
Insula (R)	839	9.3	<0.001	33	27	3
Caudate (L)	144	6.8	<0.001	-9	6	3
Caudate (R)	121	6.4	<0.001	9	9	6
Supramarginal Gyrus (R)	94	5.1	<0.001	60	-42	18
Middle Temporal Gyrus (L)	57	5.1	<0.001	-54	-54	12
Middle Frontal Gyrus (R)	30	4.4	0.006	45	27	24
Sweet Taste > Rinse						
Temporal lobe and hippocampus (L)	10032	7.6	<0.001	-30	-36	-9
Lateral occipital cortex (L)	152	4.4	<0.001	-54	-72	33
Frontal Pole (L)	149	4.5	0.011	-15	63	33
Frontal Pole (R)	30	4.9	0.020	6	60	45
Sweet Taste > Rinse						
Thalamus (L)	5103	7.0	<0.001	-3	-18	0
Oral Somatosensory cortex (L)	2065	6.3	<0.001	-21	-33	66
Anterior cingulate (L)	230	5.3	0.042	-6	39	-6
Superior frontal gyrus and paracingulate gyrus (L)	129	5.2	0.009	-9	12	51
Sweet Taste > Bitter Taste						
Hippocampus, dorsal ACC, and temporal lobe	10132	6.4	<0.001	-30	-18	-15
Oral somatosensory cortex (R)	99	5.0	<0.001	54	-6	30
Precentral Gyrus (L)	66	4.4	0.013	-3	-30	78
Orbitofrontal Cortex (R)	39	4.5	<0.001	42	33	-18
Bitter Taste > Sweet Taste						
Paracingulate Gyrus	244	5.7	0.029	6	12	48

[a] P values and cluster size (k) were calculated with FSL Randomise threshold free cluster enhancement and cluster respectively
[b] Peak coordinates are in MNI space (mm)

participants, but the differences were not meaningfully different from the null NMI distribution mean, and thus were not considered meaningfully different (Supplemental Materials). Additionally, brain response was not associated with learned preference scores (Supplemental Materials).

4. Discussion

4.1. Summary

Reinforcement learning from taste is the foundation of dietary choice, yet few studies have examined how the brain responds to taste as a primary reinforcer using a response-dependent task. Here, 85 healthy, young adults completed an instrumental conditioning task [42] to assess whole-brain response and network organization during choice and reinforcement via sweet tastes and bitter tastes. Our data suggest that choice and reinforcement via taste are associated with distinct patterns of brain response and network organization. Further, we found that BMI was associated with differential network organization of regions in the visual cortex, and that clustering of a community involved in learning and memory during choice was related to improved avoidance of a cue associated with bitter taste. Together, these results indicate that measures of brain network structure and topology are associated with individual differences in weight status and ability to learn from taste.

4.2. Appetitive PST Performance

Diverging from previous iterations of the probabilistic selection task [42,69], performance on the appetitive probabilistic selection task was close to chance in our sample. A major difference between the appetitive PST and the original version of the task is the use of sweet and bitter tasting beverages as feedback. Taste is a primary reinforcer, but

its use has challenges in research application because the motivational salience of foods change with satiation [70] and habituation to tastes [71]. Satiation, especially the development of sensory specific satiety, can decrease the motivational value of foods over time [72,73]. Further, habituation decreases operant response to rewards and punishment over exposures [71,74]. Changes to motivation over the course of the appetitive PST could contribute to the divergence of the present posttest performance from prior studies using secondary outcomes. Further, the possibility of habituation to the bitter taste or even the development of preference for the bitter taste may explain our results. Exposure increases liking of foods [75] and repeated exposure enhances the hedonic evaluation of a bitter-flavored beverage [76]. Together, sensory specific satiety and habituation may change the reward and punishment associated with sweet and bitter tastes, narrowing the difference in motivational salience between the two flavors over the course of training. In the present data posttest scores below chance (50% choose A and avoid B) could indicate the formation of preference for shapes associated with the bitter taste. Hedonic valuation of the stimuli was not assessed at the end of the task, so we are unable to directly test this interpretation, however we examined the difference in posttest performance from chance as a proxy of preference for the A or B shapes. We did not find any association between preference scores and participant characteristic or brain response to the shapes or tastants. Notably, in prior studies with non-taste outcomes, posttest performance on the PST was decreased in participants with obesity [69]. In the present sample, posttest performance was weakly negatively related to BMI, but the effect was not statistically significant. Thus, confounding effects of habituation/satiation on posttest performance may have obscured the relationship between BMI and sensitivity to outcomes in our sample.

4.3. Brain Response and Network Organization during Appetitive PST

During the appetitive PST training, we observed robust patterns of brain response across all conditions. During the choice period, including a button press in response to the question "which [shape] is correct', BOLD response was found in regions relating to these systems. BOLD response in the visual cortex, precentral gyrus, posterior temporal lobe, hippocampus and caudate, may relate to visual processing, motor response, language processing [77], working memory [78,79], and reinforcer expectations respectively [80,81]. While not all hypothesized regions showed response during choice, the observed response fits within the current model of instrumental-response in the brain [82]. Extant research on brain response to taste shows patterns of response to palatable (high sugar and high fat) tastes consistent with brain response to the sweet, reward beverage found here [27,83,84]. When reward was compared to punishment, we observed greater BOLD response in the precuneus, oral somatosensory cortex, and OFC, regions that all show response to palatable tastes compared to a neutral solution [85]. Additionally, greater response in caudate was observed, similar to other studies of palatable taste [86–88]. These results add further evidence to support brain response to palatable taste in the describe regions. When compared to sweet taste, bitter taste was associated with greater response in the dorsal anterior cingulate cortex (dACC). This result was unexpected, as we hypothesized that the bitter taste would be related to BOLD response in the OFC and amygdala. The dACC is thought to connect midbrain motivational areas to prefrontal control regions [89], and acts as a 'controller', integral for reward based decision making [90,91] and adaptation [92]. Given its role in updating response, dACC response during bitter taste receipt may reflect an update to expectations following the bitter taste.

Network organization was examined to further characterize response to the task during choice, sweet taste, and bitter taste. The brain is a complex system, and network approaches provide unique information about the coordination of brain response to a stimulus and the function of different communities, or clusters of ROIs [35].
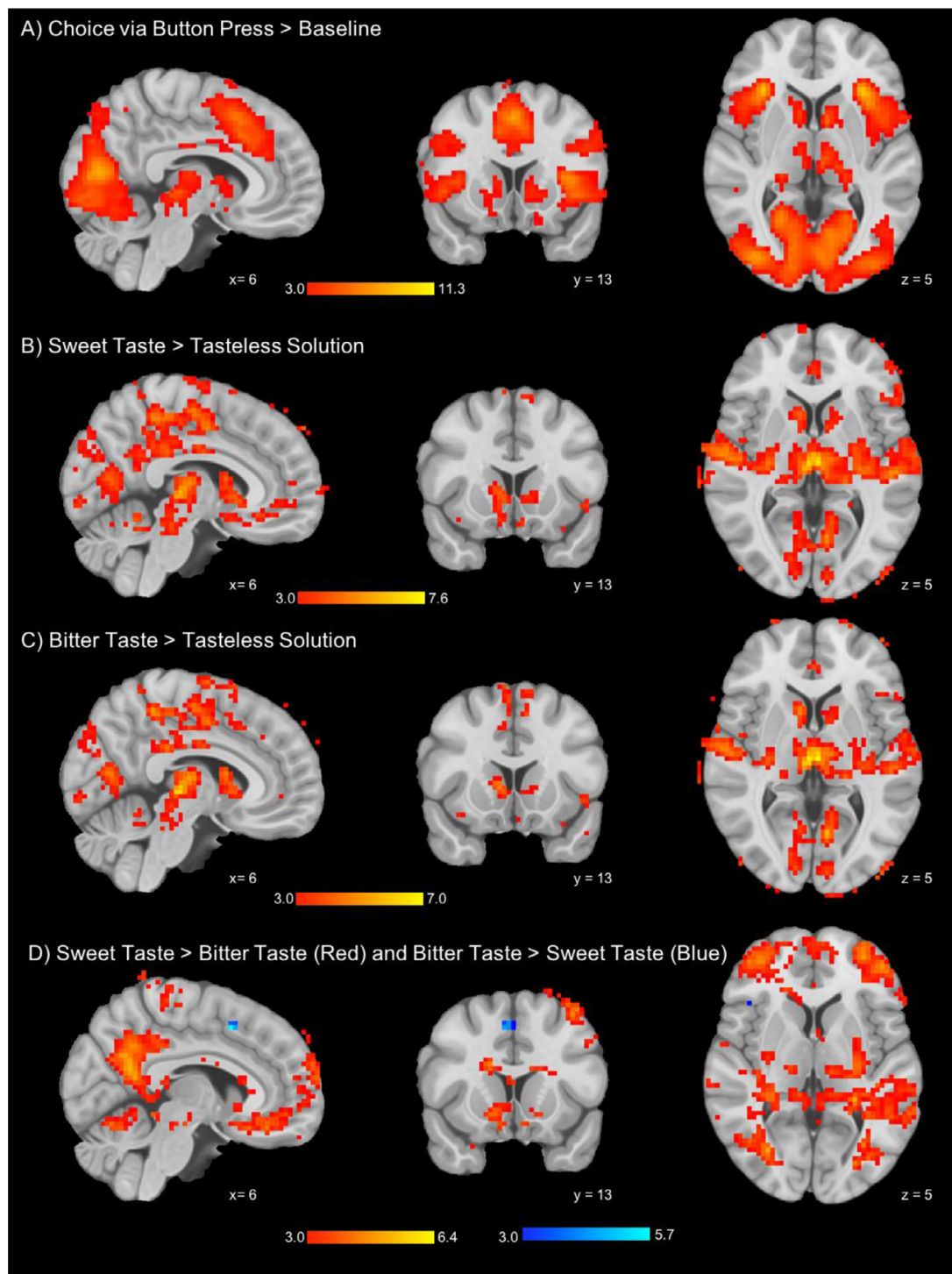
Figure 3. Brain Response During Choice, Sweet Taste, and Bitter Taste

Community structure reflects functional specialization [35], and the organization (or member assignments) of communities shed light on the subprocesses involved in cognition [93]. Across all phases of the task, we observed highly dimensional brain networks, with eight, nine, and eight communities identified during choice, sweet taste, and bitter taste, respectively. Community assignment for about 70% of the regions examined was conserved in all conditions of the task. Unique community assignment was identified for ROIs in the visual cortex and orbitofrontal cortex during choice. In this condition, ROIs in the right fusiform gyrus, intracalcarine cortex, and medial OFC organize into the same community. The medial OFC monitors stimulus-reinforcer

relationships [94]. Its connectivity with visual regions during choice may represent the incorporation of stimuli perception with reinforcer value assessment, that could underpin decisions between cues. Unique community assignment was found for ROIs in the ventromedial and ventrolateral prefrontal cortex during response to the sweet taste. During bitter taste, the vmPFC and vlPFC were grouped into a larger community with the dorsal striatum and pre/postcentral gyrus ROIs, reflecting connectivity the cortico-striatal loop that is critical for feedback-based learning and action updating [95,96]. Conversely, during sweet taste, this cortico-striatal community reorganized, such that the vmPFC was grouped with the precuneus, while the vlPFC was assigned
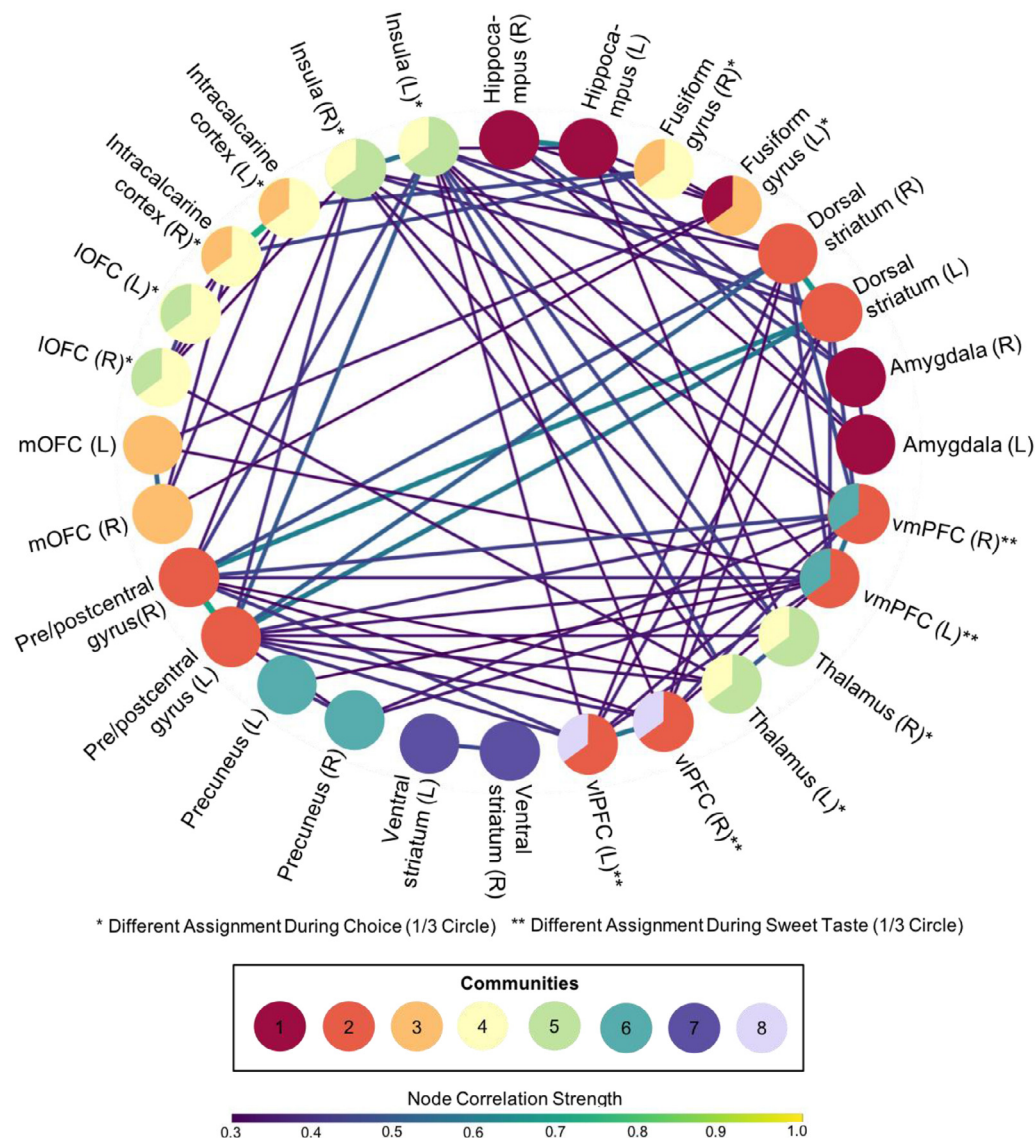
* Different Assignment During Choice (1/3 Circle)   ** Different Assignment During Sweet Taste (1/3 Circle)

Figure 4. Network Community Structure during Choice, Reward, and Punishment

to its own community. The vmPFC encodes the value of choices and outcomes [20]. The function of the precuneus is multifaceted, its response is related to self-consciousness, pain, and memory [97]. The vmPFC and precuneus are functionally connected at rest [97,98], and BOLD response in both regions increases with certainty in a choice between a desired food image and an undesired food image [99]. Increased connectivity of the vmPFC and precuneus during sweet taste may reflect the positive reinforcement conveyed by taste. Further, the vlPFC, was organized into its own community assignment during sweet taste, Dissociation of the vlPFC, which is involved in behavioral regulation [96] and learning stimulus-response relationships [100], from the vmPFC and striatum may reflect differences in the coordination of response to a sweet taste versus a bitter taste.

In consideration of the wide variance in task performance between individuals, we tested for differences in network organization and topology associated with task performance. While we did not see differences in network organization between participants who performed above chance versus below chance on the appetitive PST posttest, we found that increasing segregation of the amygdala, hippocampus, and right fusiform gyrus community during choice was significantly associated with increased sensitivity to bitter taste, as measured by the PST posttest. This community represents memory and learning regions

[101,102], and connectivity of the amygdala and hippocampus predicts behavioral adaptation to positive and negative feedback [101]. Increasing segregation of this community reflects stronger within-community connectivity and dissociation from the rest of the network [103], and allows for more efficient specialization of communities. Higher segregation may reflect more efficient communication between the areas involved in learning, memory, and visual response. This in turn, could underpin increased sensitivity to the bitter taste as observed on the posttest.

4.4. Effects of BMI on Task Performance and Network Organization

One factor demonstrated to affect PST task performance is obesity. Individuals with obesity show insensitivity to negative outcomes on the PST task [69], and more broadly obesity is related to insensitivity to negative prediction errors and punishment [104,105]. However, in the present sample we did not find significant associations between BMI and posttest performance. When network organization was compared between BMI groups, we observed differences in network organization during sweet taste between normal BMI and overweight/obese BMI groups in bilateral intracalcarine cortex ROIs and the right fusiform gyrus, where these ROIs were integrated into a broader community to

Table 4
Brain Network Communities During Choice, Sweet Taste, and Bitter Taste

Region	Coordinates (mm)			Community Assignment			Unique Community Assignment
	x	y	z	Choice	Sweet	Bitter	
Amygdala (L)	-20	-2	-22	1	1	1	-
Amygdala (R)	20	-2	-23	1	1	1	-
Dorsal striatum (L)	-12	17	-4	2	2	2	-
Dorsal striatum (R)	13	17	-5	2	2	2	-
Fusiform gyrus (L)	-33	-37	-16	1	3	3	Choice
Fusiform gyrus (R)	27	-60	-8	3	4	4	Choice
Hippocampus (L)	-26	-12	-22	1	1	1	-
Hippocampus (R)	25	-11	-23	1	1	1	-
Insula (L)	-36	2	4	5	5	5	-
Insula (R)	38	10	4	5	5	5	-
Intracalcarine cortex (L)	-8	-79	7	3	4	4	Choice
Intracalcarine cortex (R)	5	-78	7	3	4	4	Choice
Lateral OFC (L)	-30	20	-20	4	4	4	-
Lateral OFC (R)	30	20	-18	4	4	4	-
Medial OFC (L)	-14	19	-19	3	3	3	-
Medial OFC (R)	14	16	-17	3	3	3	-
Pre/postcentral gyrus (L)	-42	-17	53	2	2	2	-
Pre/postcentral gyrus (R)	40	-20	53	2	2	2	-
Precuneus (L)	-7	-59	26	6	6	6	-
Precuneus (R)	13	-62	28	6	6	6	-
Thalamus (L)	-14	-20	0	5	5	5	-
Thalamus (R)	14	-20	0	5	5	5	-
Ventral striatum (L)	-10	17	7	7	7	7	-
Ventral striatum (R)	10	16	7	7	7	7	-
Ventrolateral PFC (L)	-42	46	-1	2	8	2	Sweet
Ventrolateral PFC (R)	43	48	-6	2	8	2	Sweet
Ventromedial PFC (L)	-5	43	-8	2	6	2	Sweet
Ventromedial PFC (R)	6	42	-4	2	6	2	Sweet

the left fusiform gyrus and medial OFC in the overweight/obese group. Thus, during sweet taste, network organization among overweight/obese participants reflect increased connectivity of visual ROIs with the orbitofrontal cortex during sweet taste. Similarly, Geha et al reported increased global connectivity of the visual cortex in obesity during consumption of a palatable milkshake [106]. Further, obesity is associated with stronger visual cortex response to food images [107]. Our results also support the interpretation that elevated BMI may be related to greater orientation to external stimuli during consumption [106], which could contribute to excessive intake.

4.5. Limitations

This study has notable strengths and limitations. While our study is the first to adapt the Probabilistic Selection Task to use a primary taste reinforcer, we were not able to reliably identify learning in our sample. While the two tastants were selected to serve as a reward and punishment, the lack of evidence for learning on the posttest suggest that tastants may not have provided the intended reinforcement during the training. Because of this, we were not able to account for learning and expectancy in our analyses of BOLD response and network structure during training. It is possible that response, especially that of midbrain ROIs that respond strongly to prediction error [17,108] may be misattributed to response to reward or punishment. Within individuals, this may not impact overall results because prediction error should be distributed across sweet taste and bitter taste evenly, but across individuals this effect may be meaningful, since feedback was randomized, and participants received different numbers of prediction error trials (e.g. choose correct shape, but received bitter taste). While the rate of prediction error trials was not correlated with posttest accuracy, it may have contributed to differences in trial-by-trial brain response. Future studies of brain response during taste-mediated instrumental conditioning should aim to increase the number of taste events or include additional training to improve performance and allow for a computational model of reinforcement learning to be fit to behavioral data. Second, graph-theory based network analyses provide unique

information to further characterize brain response during choice, sweet taste administration, and bitter taste administration. However, these types of analyses limit the scope of brain regions examined. While the ROIs selected were drawn from research on reinforcement learning and taste administration, it is possible that regions meaningful to network structure were not included in our analytic set. With more trials, future studies may be able to identify other regions important to network structure during choice, reward, and punishment. Similarly, we did not observe any meaningful differences between participants who performed above chance on the posttest and those who performed below chance. Some unmeasured construct may relate to individual differences in posttest performance, such as impulsivity [109] or episodic memory [110]. Finally, this study did not collect hedonic ratings of the task stimuli following completion of the PST training. Without this data we are not able to test for changes in the motivational salience of the sweet taste and bitter taste following training, limiting our ability to address the possible effects of satiation or habituation to the taste on posttest performance.

5. Conclusions

How we learn from taste reinforcement is an important driver of food choices, and provides a window into how food may motivate individuals to choose palatable foods. Our results are the first to examine network community structure during completion of an instrumental conditioning task with response-dependent taste administration. We found that brain networks during choice, sweet taste and bitter taste are similar, with key differences in visual cortex areas and prefrontal regions important for value representation and behavioral regulation. We found that during sweet taste, participants with overweight/obese BMI showed broader connectivity of visual cortex regions than participants with normal BMI, suggesting that elevated BMI is related to greater integration of external stimuli during consumption. Also, segregation of a community involved in learning and memory was associated with improved posttest performance, indicating that efficient processing within this community is associated with an improved ability to avoid
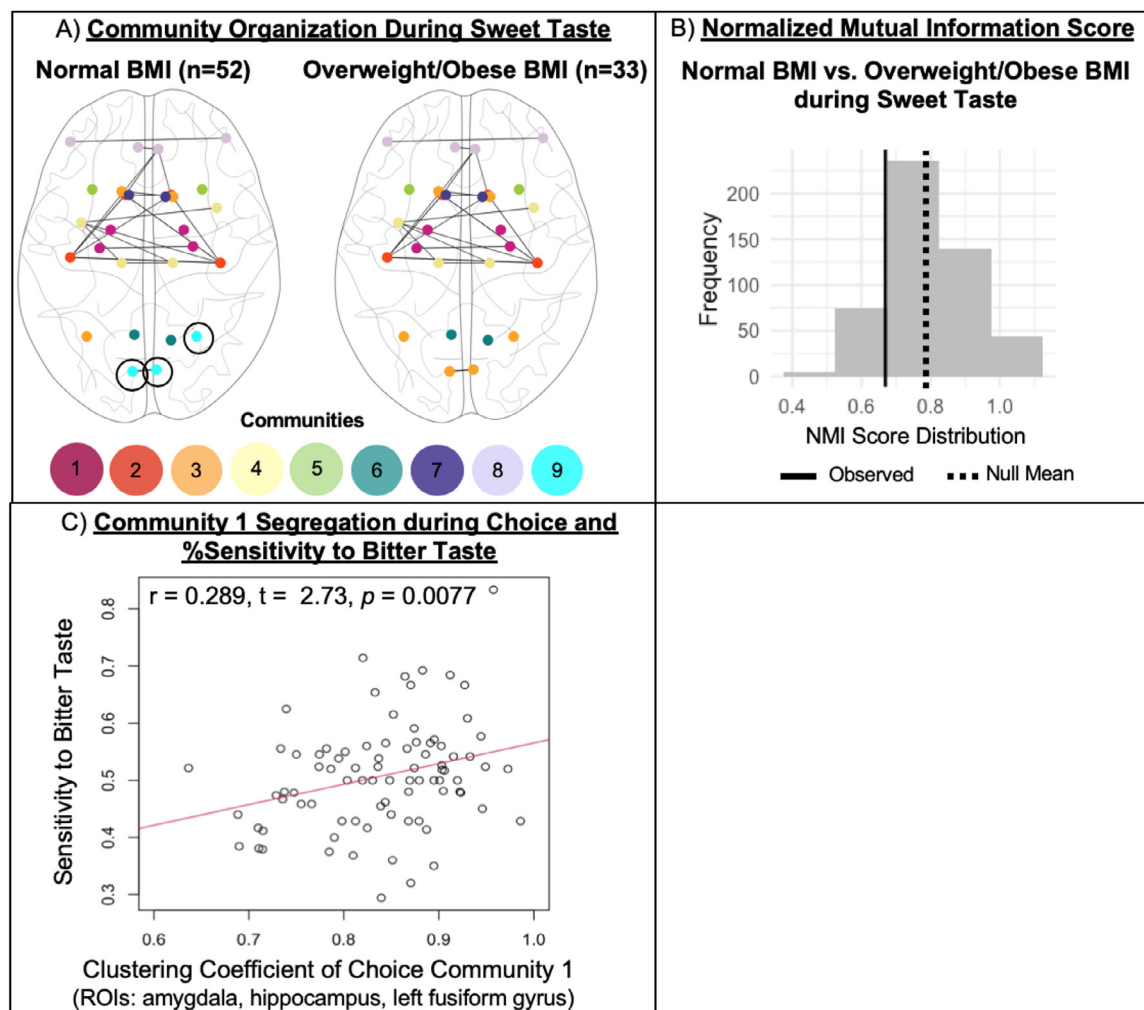
A) Community Organization During Sweet Taste

B) Normalized Mutual Information Score

C) Community 1 Segregation during Choice and %Sensitivity to Bitter Taste

Figure 5. Differences in Community Structure and Metrics associated with BMI and Posttest Performance.

bitter tastes. Together, results shed light on the complex interaction of brain regions responding to taste-based reinforcement, support that individual differences in connectivity of visual regions and segregation of learning and memory areas are related to BMI and brain response to taste.

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Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2020.112962.

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