ORIGINAL ARTICLE

Extremes of Eating Are Associated with Reduced Neural Taste Discrimination

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ABSTRACT

Objective: Eating disorders are severe psychiatric disorders of unknown etiology. Understanding how neuronal function affects food choices could help personalize treatment based on brain function. Here we wanted to determine whether disordered eating behavior is associated with alterations in the primary taste cortex's ability to classify taste stimuli, which could interfere with taste reward processing.

Method: One-hundred and six women, 27 healthy comparison (age 26.15 ± 6.95 years), 21 with restricting-type anorexia nervosa (AN; age 23.10 ± 6.14 years), 19 recovered from restricting-type AN (recovered AN; age 26.95 ± 5.31 years), 20 with bulimia nervosa (BN; age 25.15 ± 5.31 years), and 19 with obesity (age 28.16 ± 8.13 years), received sucrose, control solution or no taste stimulation during functional magnetic resonance brain imaging. Multivariate Bayesian pattern analysis (decoding) and cross-validation tested taste classification accuracy (adjusted for comorbidity, medication use, taste perception, interoception, and brain activation volume).

Results: For sucrose versus control solution, classification accuracy differed ($F = 2.53$, $p < 0.041$). *Post hoc* tests indicated higher classification accuracy in healthy comparison compared to women with AN ($p < 0.016$) or obesity ($p < 0.027$), and in recovered AN as compared to AN ($p < 0.016$) or obesity ($p < 0.047$) groups. Taste stimulation resulted in sparse insula voxel activation across all groups.

Discussion: Reduced classification accuracy across stimuli in women with AN or obesity could indicate low brain encoding discrimination of stimulus quality, which could contribute to altered reward activation and eating drive that is not adjusted to nutritional needs. This deficit appears to normalize with recovery from AN, but adjusting food flavor intensity could aid in the treatment of individuals with AN or obesity. © 2016 Wiley Periodicals, Inc.

Keywords: anorexia; bulimia; classification accuracy; obesity; taste; insula; recovery; decoding

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Introduction

Eating disorders (EDs) are severe psychiatric disorders,[1] with anorexia nervosa (AN) characterized by fear of weight gain and underweight, and bulimia nervosa (BN) by binge eating and purging but normal weight.[2] Usually associated with more food intake than physiologically needed is obesity, defined by a body mass index (BMI, kg/m^2) ≥30. EDs and obesity are associated with increased mortality,[3,4] their underlying causes are considered multifactorial and treatment success is modest.[4–8]

Basic science and human *in vivo* brain imaging research has suggested that food restriction and overeating are associated with alterations in reward circuit function.

Taste is an important driver of food intake[9] and invariably associated with distinct neuronal patterns in the insula, the brain's primary taste cortex.[10] The insula connects to ventral striatum, orbitofrontal cortex, and amygdala, higher order brain structures that control how much we eat.[11,12] Thus the insula has a "gate-keeper" function for taste information transmission and could have a central role in the pathophysiology of disordered eating.[13] The insula is also important for interoceptive awareness [responding to body cues[14]], which tends to be altered in EDs.[13]

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Insula *size* is altered in EDs,[15,16] and *functional* alterations in the insula have also been reported repeatedly. For instance, in AN after recovery, insula, anterior cingulate, and striatal activation was reduced during repetitive sucrose application,[17] but insula and cingulate response was increased when applied randomly.[18] In BN, sucrose and milkshake activated insula and frontal cortex was less than in CW.[19,20] Imaging research in obesity most commonly implicated the insula,[21] with increased or decreased activation depending on anticipation or receipt of visual or actual food stimuli.[22,23]

Functional brain imaging typically studies strength of activation (dependent variable) in response to specific stimuli (independent variable) and may inform on specific brain circuits.[24,25] The measured signal is the sum of many neurons coming together, although some neurons may contribute much and others little to the overall signal. In contrast, so called multivariate (multi-voxel) pattern analysis, or decoding, goes the opposite direction and uses brain activation patterns as the independent variable to classify task conditions.[26–28] Multivariate pattern analysis is used to investigate how brain regions code stimuli-specific information as distinct patterns of neural activity. This then allows for differentiation of distinct perceptual states by assessing the characteristic distribution of voxel activation. Thus, decoding tries to identify a neuronal "fingerprint" to predict a condition or psychological state.[24,29] However, there may be many equally likely solutions of voxel activation patterns, and to overcome this problem, one can use constraints or priors in a multivariate Bayesian approach, by testing how voxel patterns are distributed within predefined models.[26,27] Crossvalidation then can test the brain's "pattern classification accuracy", or how well a person's distinct activation pattern (associated with the stimulus or psychological state) can be generalized to the full data set, which can be compared across individuals and groups.

Various studies have applied decoding strategies to brain activation. For instance, decoding has been used in the study of vision, finding that distinct activation patterns could predict discrete objects.[30] Decoding was also used to study attention states, memory generation, decision making bias and lie detection,[31,32] as well as interoception of pain, which could be relevant for ED research.[13] To the best of our knowledge decoding has not been studied previously in EDs or obesity.

Here we tested the hypothesis that insula taste classification accuracy is reduced in individuals with disordered eating behavior. We sought to (1) determine the best model of pattern activation in this region across participants and (2) compare taste classification pattern accuracy between groups, while correcting for potential confounds such as comorbidity, medication use, brain volume, but also interoceptive or taste perception differences, factors that may fluctuate with anxiety and self-restraint.[33,34] We anticipated two possible scenarios. One, AN could be associated with higher and obesity with lower pattern classification accuracy with the idea that under- and overweight are associated with higher and lower response to food stimuli.[23] Alternatively, having in mind that AN and obesity may respond stronger or weaker to *any* type of stimulus, both groups might distinguish taste stimuli poorly as they may code stimulus salience similarly high or low. We studied two additional groups, individuals recovered from AN to test whether such deficits would improve with recovery, and individuals with BN to strengthen the hypothesis that any alterations seen are more dependent on weight or other biologic factors than simply on ED cognitions.

Methods

Study Participants

We recruited 106 women, 27 healthy comparison women (CW), 21 women with restricting-type AN, 19 women recovered from restricting-type AN, 20 women with BN, and 19 women with obesity (**Table 1**). The Colorado Multiple Institutional Review Board approved the study; all participants gave written informed consent. Participants received $160 for the brain imaging session and completion of assessments.

AN[35] was defined as underweight below 85% of weight expected for age and height, severe fear of gaining weight, body image distortion, lack of menstrual cycle, but without binge eating/purging behavior. Individuals with BN had binge eating/purging episodes at least twice per week for at least three months and self-evaluation was unduly influenced by shape and weight. Obesity was defined by BMI $\geq$30.[36] Individuals recovered from AN had a history of restricting-type AN, normal weight, regular menses, and normal exercise patterns for $\geq$1 year. Healthy CW had no history of psychiatric or major medical illness, were not taking medication, and were within normal BMI range life long.

Individuals with AN or BN were within their first 1–2 weeks of inpatient or partial hospitalization treatment, and had no electrolyte, blood count or other laboratory abnormalities. A doctoral level interviewer assessed psychiatric diagnostic status using the structured clinical interview (SCID[35]) for DSM-IV diagnoses. CW, women

TABLE 1. Demographic variables

	Healthy Comparison Women (A)		Women with Anorexia Nervosa (B)		Women with Bulimia Nervosa (C)		Women with Obesity (D)		Women Recovered from Anorexia Nervosa (E)				
	n = 27		*n* = 21		*n* = 20		*n*=19		*n* = 19				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	*p* values	
Age (years)	26.2	7.0	22.9	6.1	25.2	5.3	28.2	8.1	27.0	5.3	1.9	0.115	n.s.
BMI (kg/m^2)	21.5	1.4	16.0	1.1	22.6	5.7	34.7	4.6	20.2	1.1	89.0	<0.001	A, C, D, E>B***; A>E**; A, C, E<D***
Novelty seeking	18.5	5.3	13.8	6.8	22.1	6.7	21.2	5.5	17.5	5.8	6.1	<0.001	B<C, D**
Harm avoidance	9.9	4.1	22.7	6.6	23.0	5.8	12.6	5.9	15.4	7.2	22.6	<0.001	B, C>A, D***; B, C>E*
Depression	1.3	1.0	23.5	9.8	24.5	11.4	4.8	4.6	3.8	3.6	56.1	<0.001	A, D, E<B, C***; A<D*
Interoceptive deficits (EDI-3)	1.0	1.6	16.0	7.7	18.2	6.2	6.1	9.3	3.8	5.1	32.4	<0.001	A<B, C***; B>D**, E***; C>D, E***
Drive for thinness (EDI-3)	2.5	3.3	19.5	5.9	23.1	4.5	13.1	8.4	8.3	6.0	48.8	<0.001	A<B, C, D***; A<E**; B, C>E***; B>D***
Bulimia (EDI-3)	1.0	1.4	3.5	3.9	22.7	5.3	12.0	11.9	2.2	2.4	50.2	<0.001	A, B, E<C***; A<D**; D<C*; D>E*
Body dissatisfaction (EDI-3)	4.0	4.2	24.8	8.9	30.7	8.0	26.6	9.0	9.6	6.5	56.4	<0.001	A, E<B, C, D***; A<E*
Punishment sensitivity	4.2	1.8	12.8	4.7	12.4	3.9	6.9	4.5	7.1	4.1	21.6	<0.001	A<B, C***; D, E<B, C**
Reward sensitivity	4.5	2.9	7.5	3.6	8.4	3.7	6.3	4.6	6.4	3.4	3.9	0.006	A<B*; A<C**
State anxiety	26.0	5.4	52.7	11.5	50.1	13.8	31.8	10.9	32.2	13.3	26.0	<0.001	A, D, E<B, C***
Trait anxiety	28.3	5.7	54.9	11.7	58.0	11.1	35.3	9.7	34.8	11.0	39.5	<0.001	A, D, E<B, C***
Sucrose sweetness	5.2	2.3	4.5	2.5	5.5	2.9	4.1	2.5	5.1	1.9	1.1	0.362	n.s.
Sucrose pleasantness	8.4	0.8	8.6	0.6	8.7	0.6	8.3	1.2	9.2	1.0	1.2	0.336	n.s.
SU-AS-Number activated voxels	159.4	74.0	180.0	97.0	165.4	72.8	174.8	75.5	143.5	46.5	0.7	0.587	n.s.
SU-NO-Number activated voxels	261.9	28.7	257.6	48.9	274.5	70.1	247.6	48.9	241.3	59.4	1.2	0.304	n.s.
AS-NO-Number activated voxels	248.3	47.6	238.1	65.0	246.0	63.2	246.3	52.2	256.0	55.2	0.3	0.905	n.s.
	N		*N*		*N*		*N*		*N*				
Medication use													
SSRI	0		9		9		0		3				
Atypical antipsychotic	0		2		0		0		0				
SSRI + Atypical Antipsychotic	0		1		4		0		0				
Comorbid diagnoses													
Major depression	0		3		3		0		3				
Anxiety disorder	0		4		6		0		3				
Major depression + Anxiety disorder	0		5		7		0		1				

BMI, body mass index; EDI-3, Eating Disorder Inventory 3; SSRI, selective serotonin reuptake inhibitor; SU-AS, sucrose vs. artificial saliva; SU-NO, sucrose vs. no solution; AS-NO, artificial saliva vs. no solution.

recovered from AN, women with BN or obesity were studied during the first ten days of the menstrual cycle to keep hormonal variation low.[37]

Psychological Assessments

Study participants completed self-assessments for: (1) drive for thinness, bulimia, body dissatisfaction and interoceptive deficits (Eating Disorder Inventory-3)[38]; (2) harm avoidance (Temperament and Character Inventory)[39]; (3) state and trait anxiety (Spielberger State and Trait Anxiety Inventory)[40]; (4) depression (Beck Depression Inventory)[41]; and (5) reward and punishment sensitivity (Sensitivity to Reward and Punishment Questionnaire, revised).[42]

Brain Imaging Procedures

Prior to breakfast, participants rated randomly presented, unmarked taste stimuli (distilled water; five sucrose solution strengths, Mallinckrodt Chemicals, Phillipsburg, NJ: 2%, 4%, 8%, 16%, 1*M*; and artificial saliva: 25 m*M* KCl, 2 m*M* $NaHCO_3$)[43] for sweetness, 'absent'[1] to 'extreme'[9], and pleasantness, 'dislike extremely'[1] to 'like extremely'[9], on 9-point Likert scales. Between 7.00 and 8.00 AM, AN, and BN groups ate breakfast according to their meal plan, comparison, obese, and women recovered from AN had breakfast matched to the average ED program meal plan breakfast. Blood oxygen level dependent functional magnetic resonance brain imaging (fMRI) was performed between 8.00 and 9.00 AM (GE Signa 3T scanner, T2* weighted echo-planar imaging, voxel size 3.4 × 3.4 × 2.6 mm, TR 2100 ms, TE 30 ms, angle 70°, 30 slices, interleaved acquisition, and 2.6 mm slice thickness with 1.4 mm gap).

Taste Task

Individuals received three taste stimuli during fMRI imaging[43]: 1 mol/L sucrose solution (100 trials), no solution (100 trials), and artificial saliva (80 trials). Individuals learned to associate each taste stimulus with a paired conditioned visual stimulus (CS) that is probabilistically associated with its unconditioned stimulus (US): the no-solution (null) CS was followed in 20% of trials by sucrose (unexpected sucrose receipt, positive-prediction error), and the sucrose CS was followed in 20% of trials by no-solution (unexpected Sucrose omission, negative-prediction error). The first 10 trials were fixed CS shape for sucrose followed by US sucrose delivery to establish an initial stable association between the CS sucrose shape and US sucrose taste.[43] Trials began with the CS (2 s), followed by US delivery, tongue swish and swallow and awaiting the next trial (4 s). Each trial lasted 6 s. Every 2.1 s a brain image was recorded. All other trials were fully randomized. Taste stimuli were applied using a customized programmable syringe pump (J-Kem Scientific, St. Louis, MO) controlled by E-Prime Software (Psychological Software Tools, Pittsburgh, PA) and triggered by MRI-scanner radiofrequency pulse.[19] Task duration was 28 min. We only included trials with matching CS–US association in order to focus on taste classification and reduce effects from the prediction error response.

Brain Imaging Analysis

Brain-imaging data were preprocessed and analyzed using Statistical Parametric Mapping software (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Images were realigned to the first volume, normalized to the Montreal Neurological Institute template, and smoothed with a 6 mm FWHM Gaussian kernel.[44] Image sequences were manually inspected and images with artifacts or movement >1 voxel removed. Data were modeled with a hemodynamic response convolved boxcar function, using the general linear model, including temporal and dispersion derivatives, autoregression, and 128 s high-pass filter.

We computed three first level contrasts for each subject: (1) sucrose versus no solution; (2) artificial saliva versus no solution; (3) sucrose versus artificial saliva.

Analysis 1 (group by condition ANCOVA):

To test whether groups differed in insula activation strength, we used a random effects, whole brain analysis ($p < 0.05$ family-wise error corrected (FWE), cluster size $\geq$5 voxels).[23]

Analysis 2 (Multivariate Bayes, MVB, Decoding Analysis):

Step 1. In the MVB approach[27] the first step is to identify the optimal model of activation distribution in the relevant brain region. The prediction is that brain activation is distributed according to a sparse model solution. The area of interest on the functional images and for the contrasts of interest are identified (from the taste activation task). The next step is a "greedy search" procedure. Here the algorithm's goal is to detect the best model of activation distribution in relation to the task condition. The brain region of interest is partitioned into subsets of increasing size and tested for type of activation distribution: In a sparse model few voxels have large variance while most have small variance. In a smooth model, there is a sparse representation of activation that is spatially coherent over the brain anatomy. The support model is a type of distributed model where each pattern is an individual voxel and a large number of distributed patterns are expressed. The sparse, support, and smooth MVB models were tested for each of the three contrasts of interest (1) expected sucrose contrasted against expected no solution; (2) expected sucrose contrasted against expected artificial saliva; (3) expected artificial saliva contrasted against expected no solution) for each participant. Expectation–maximization (EM) uses the highest voxel weights for fitting the model. This method

creates the log-evidence value. The solution with the largest log-evidence indicates the optimal set of activation distribution. EM algorithms can be prone to overfitting with higher order polynomials. However, this problem is reduced with increasing number of data points and the fMRI study and each condition (sucrose, artificial saliva, no-solution) had 80 trials with 228 images across those 80 trials should provide adequate number of data points.[45]

Step 2. After delineation of the adequate distribution model, the log evidence can then be used for cross-validation to identify classification accuracy. Cross-validation partitions data into subsets so that the analysis is performed on one (training) subset, while the other (test) data are retained to confirm and validate the initial analysis. In *k*-fold cross validation, data is randomly partitioned into *k* partitions, training the classifier on all but one and evaluates classification performance on that partition. This procedure is repeated for all *k* partitions (here $k = 8$). Cross-validation prediction accounts properly for serial correlations and confounds by ensuring that the cross-validation weights cannot be influenced by test data and that the prediction is conditionally independent of the training data. Classification accuracy was then compared across groups.

While there are other classification algorithms such as support vector machine or Gaussian models, we chose MVB for various reasons. We were not interested whether brain response can separate patients from CW, which is a typical goal of classification algorithms. Rather MVB tests different distribution models and compares the model evidence for each participant. Other methods base their analysis on the expectation that a sparse model is at hand. In light of different volumetric measures of the insula across eating disorders we wanted to make sure that we test various models in the eating disorder groups and use the most accurate data for cross-validation.

Statistical Analysis

Behavioral data (ANOVA) and classification accuracy (univariate general linear model including factors and covariates, ANCOVA) were analyzed with SPSS-22 software (IBM-SPSS, Chicago, IL). *Post hoc* group comparisons were assessed with Dunnett's T3, and estimated marginal means were computed for classification accuracy and multiple-comparison corrected using bootstrap. Several variables were hypothesized a priori to be possible confounds and included in the between-group model (5 group ANCOVA, CW, AN, BN, recovered AN, obese individuals): number of activated voxels (adjusting for volume differences), interoceptive deficits, sweetness perception of control solution as well as sucrose solution; in addition comorbid anxiety and depression diagnoses and medication use were included as factors in the model. Pearson correlation analysis tested brain-behavior correlations. Sweetness perception across sucrose concentrations was tested with repeated measures ANOVA.

Results

Demographic Variables (Table 1)

Age was similar between groups. BMI was higher in obesity and lower in AN and recovered AN groups as compared to CW. Interoceptive deficits, harm avoidance and state and trait anxiety were higher in AN and BN groups as compared to CW, depression scores were elevated in AN, recovered AN and BN. Drive for thinness and body dissatisfaction were elevated in all groups as compared to CW, bulimia scores were elevated in BN and obesity. Sweetness and pleasantness perception were similar between groups, as was slope for sweetness perception across concentrations ($F = 0.819$, $p < 0.516$). Some individuals with AN or BN had comorbid psychiatric disorders or were on medication.

Analysis 1 (group by condition ANCOVA):

The 5-group by 3-taste condition contrast including covariates depression, anxiety, and medication use, with and without interoceptive deficits or sweet taste perception did not result in significantly different insula activation; however within groups, all contrasts showed positive posterior and mid insula activation.

Analysis 2 (Multivariate Bayes, MVB, Decoding Analysis):

Classification accuracy (mean ± SEM) for sucrose versus no solution (CW:70.7 ± 1.6; AN:70.5 ± 1.3; BN:68.9 ± 1.4; obesity:68.8 ± 1.4; Recovered AN:69.7 ± 1.5) was not significantly different between groups (df = 4, $F = 0.615$, $p < 0.7$). Classification accuracy for artificial saliva versus no solution (CW: 70.2 ± 1.4; AN:69.8 ± 1.2; BN:70.3 ± 1.3; obesity:69.9 ± 1.2; recovered AN:69.5 ± 1.3) was also not significantly different across groups (df = 4, $F = 0.109$, $p < 0.9$).

Sucrose versus artificial saliva classification accuracy differed significantly across groups (df = 4, $F = 2.601$, $p < 0.041$), with lower classification accuracy (mean ± SEM) in AN (56.6 ± 0.8; $p < 0.016$) and obesity (58.1 ± 0.9; $p < 0.027$) as compared to CW (60.4 ± 1.0), and lower values ($p < 0.047$) for AN versus recovered AN (60.0 ± 0.9; $p < 0.016$) and obesity versus recovered AN. BN

FIGURE 1 Distributed sparse coding pattern of insula activation rendered on template brain across exemplary participants from each study group. (A) High classification accuracy; (B) Low classification accuracy. CA, classification accuracy. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

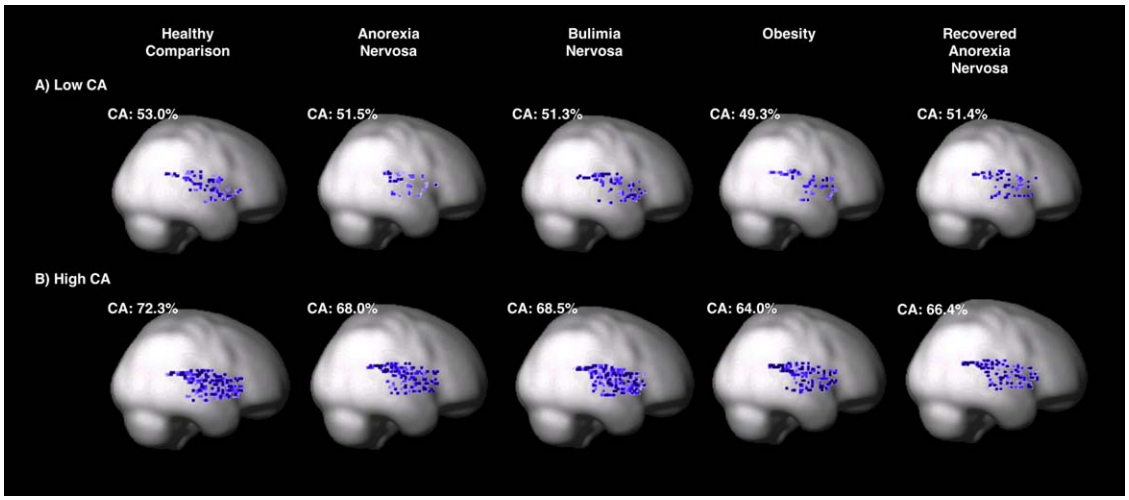
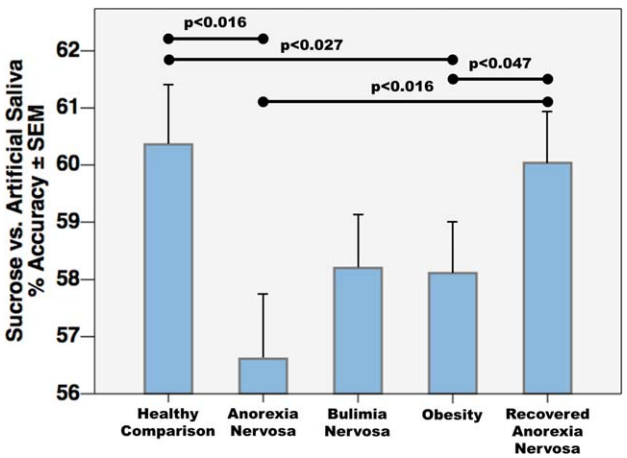


FIGURE 2 Classification accuracy across groups. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



(58.20 ± 0.89) did not differ significantly from any group (**Fig. 1**). The voxel weights in each group were significantly greater for sparse versus smooth or support distribution (**Fig. 2**, Supporting Information Fig. 1): CW sparse 79.2 ± 45.4, smooth 13.1 ± 17.4, support 8.2 ± 14.4, $F = 49.5$, $p < 0.001$; AN sparse 75.0 ± 50.6, smooth 17.9 ± 28.3, support 12.0 ± 24.1, $F = 19.4$, $p < 0.001$; BN sparse 79.0 ± 43.8, smooth 17.5 ± 23.7, support 9.8 ± 19.2, $F = 30.3$, $p < 0.001$; obesity sparse 75.4 ± 34.1, smooth 11.5 ± 11.6, support 5.2 ± 9.4, $F = 62.7$, $p < 0.001$; recovered AN sparse 74.2 ± 37.1, smooth 15.0 ± 20.2, support 7.8 ± 20.7, $F = 34.2$, $p < 0.001$.

Correlation Analyses (Table 2)

CW: Classification accuracy for sucrose versus artificial saliva contrasts correlated positively with number of activated voxels (261.9 ± 28.7; $r = 0.688$, $p < 0.001$) and negatively with sucrose sweetness perception ($r = -0.527$, $p < 0.005$).

AN: Classification accuracy for sucrose versus artificial saliva was positively correlated with number of activated voxels (257.6 ± 48.9; $r = 0.712$, $p < 0.001$).

Recovered AN: Classification accuracy for sucrose versus artificial saliva was positively correlated with interoceptive deficits ($r = 0.550$, $p < 0.015$).

BN: Classification accuracy for sucrose versus artificial saliva was positively correlated with number of activated voxels (274.5 ± 70.1; $r = 0.679$, $p < 0.001$); classification accuracy for sucrose versus no solution correlated negatively with sucrose sweetness ($r = -0.690$, $p < 0.001$).

Obesity: Classification accuracy for sucrose versus artificial saliva correlated positively with number of activated voxels (247.6 ± 48.9; $r = 0.853$, $p < 0.001$) with a tendency to positive correlation with interoceptive deficits ($r = 0.425$, $p < 0.070$).

Discussion

This study indicates that AN and obesity are associated with reduced taste classification accuracy in the insula when contrasting caloric sucrose against a control solution. Pattern classification accuracy

TABLE 2. Correlation results

Population		Pearson Correlation	EDI3-ID	P AS	S AS	P 1M SU	S 1M SU	Significantly activated voxels SU-AS	SU-NO	AS-NO
Healthy CW	SU-AS % accuracy	*r*	0.028	0.254	−0.135	0.25	−0.527**	0.688***		
		p	0.89	0.202	0.502	0.208	0.005	<0.001		
	SU-NO % accuracy	*r*	−0.198			−0.163	−0.094		−0.037	
		p	0.322			0.417	0.639		0.854	
	AS-NO % accuracy	*r*	−0.11	0.021	−0.031					0.075
		p	0.584	0.917	0.878					0.709
Women with AN	SU-AS % accuracy	*r*	−0.143	−0.071	0.178	−0.22	−0.186	0.712***		
		p	0.536	0.76	0.44	0.337	0.419	<0.001		
	SU-NO % accuracy	*r*	0.318			−0.209	0.135		−0.401	
		p	0.16			0.363	0.56		0.072	
	AS-NO % accuracy	*r*	0.246	−0.208	−0.01					0.797***
		p	0.283	0.367	0.964					<0.001
Women with BN	SU-AS % accuracy	*r*	−0.193	0.561*	1	0.126	0.093	0.679***		
		p	0.414	0.01	.	0.596	0.697	<0.001		
	SU-NO % accuracy	*r*	−0.212			−0.04	−0.187		0.32	
		p	0.37			0.868	0.431		0.17	
	AS-NO % accuracy	*r*	−0.403	0.134	1					0.396
		p	0.078	0.572	.					0.084
Women with obesity	SU-AS % accuracy	*r*	0.425	−0.168	0.143	0.16	0.259	0.853***		
		p	0.07	0.492	0.559	0.512	0.284	<0.001		
	SU-NO % accuracy	*r*	0.17			−0.04	−0.238		0.071	
		p	0.487			0.871	0.326		0.771	
	AS-NO % accuracy	*r*	0.013	0.125	0.175					−0.153
		p	0.958	0.611	0.474					0.531
Women recovered from AN	SU-AS % accuracy	*r*	0.550*	0.196	0.098	0.088	0.021	0.217		
		p	0.015	0.422	0.691	0.721	0.932	0.372		
	SU-NO % accuracy	*r*	0.016			−0.093	−0.074		0.33	
		p	0.949			0.706	0.763		0.168	
	AS-NO % accuracy	*r*	0.233	0.162	0.023					0.799***
		p	0.338	0.506	0.926					<0.001

AN, anorexia nervosa; BN, bulimia nervosa; CW, comparison women; EDI3-ID, Eating Disorder Inventory 3 Interoceptive Deficits; PAS, Artificial saliva pleasantness rating; SAS, Artificial saliva sweetness rating; P 1 M SU, 1 molar sucrose pleasantness rating; S 1M SU, 1 molar sucrose sweetness rating; SU-AS, sucrose versus artificial saliva; SU-NO, sucrose versuss no solution; AS-NO, artificial saliva versus no solution.

in recovered AN and BN did not differ significantly from the CW group and suggests that taste classification accuracy alterations could be adaptations to an abnormal eating and weight state.

The overall accuracy of insula pattern classification between 50% and 70% may seem low but is comparable with other studies that investigated brain pattern classification.[46,47] Larger regions of interest are used for decoding and pattern classification and typically result in higher classification accuracy; we selected the bilateral insula as a larger yet anatomically defined region. There was no group difference in classification accuracy for sucrose or control solution tested against no solution. This suggests that the perceptual state to sucrose or control solution applied individually, which includes taste perception but also general sensory information, is encoded adequately in AN and obesity. However, when directly contrasting the two taste stimuli, to remove effects of texture and other sensory stimulation in the mouth, encoding differences more specific to taste quality become apparent. Thus there may be deficits in neuronal encoding of distinct taste qualities in AN and obesity, but this may remit with recovery from AN as in our recovered sample. Those results seem to be in line with previous studies. Perception of individual taste stimuli in EDs was not altered,[48] but research indicated lower olfactory or gustatory stimulus *discrimination* in EDs.[49] Some studies in obesity have also shown difficulties with taste differentiation,[50] and sweet taste sensitivity increases with weight-reduction in obesity.[51,52]

What determines such alterations could occur on a variety of levels. For instance, leptin and other hormones are altered in EDs and obesity and affect taste perception[53–55]; reduced insula pattern classification could be due to primary structural changes *within* the insula,[15] or alternatively could result from altered taste signal processing in afferent pathways *to* the insula.[56]

The insula has repeatedly been implicated in ED and obesity pathophysiology.[13,17–21,23,57,58] The bilateral anterior and middle insula responds to taste stimulation[59] and transmits information to ventral striatal and orbitofrontal reward pathways.[11] The anteroventral insula is connected to the amygdala[12] and aids in generating internal emotional states.[60]

Especially the *right* anterior insula has been associated with self-recognition, "abstract representation of oneself"[61] and interoceptive awareness.[62] *Left* anteroventral insula activation is related to gastric distention[14] and self-reported fullness.[63] Thus, many intertwined functions are processed and alterations on different levels within the insula could contribute to our findings.

Altered insula function could have important clinical implications. If normal taste discrimination is disturbed, then it is possible that normal insula inputs to basal ganglia and higher order taste processing are altered.[64] Subsequently, other circuits such as subcortical reward or prefrontal cognitive-emotional circuits could have greater influence on determining the drive to eat or not eat. AN and obesity have been associated with altered dopamine related reward function,[23] elevated or reduced cognitive control[65,66] as well as high anxiety,[67] and disturbances in those circuits could increasingly drive eating pathology the more afferents from the insula are altered. In fact, such a "multifaceted" concept for behavior modulation has been suggested previously for the psychopathology of obesity.[68] Hypothetically, if individuals with AN and obesity do not receive appropriate insula signals in response to taste stimuli but basal ganglia dopamine hyper-(AN) or hypo-(obesity) activation respectively have a stronger impact on food choices, then it could be possible that reducing flavor intensity during treatment of AN and enhancing flavor for obesity could counteract those subcortical mechanisms. Normal insula classification accuracy in the recovered AN group provides hope that classification accuracy alterations do improve with recovery.

Limitations

We can only speculate at this point why AN as well as obesity groups showed similarly reduced classification accuracy when contrasting sucrose versus artificial saliva. Response to taste stimuli may be similarly increased or decreased across stimuli in AN or obesity[18,23] and the result when contrasting stimuli against each other may be for each case reduced classification accuracy. This will require further research. We included medication use and comorbid conditions as covariates in the analysis but cannot exclude entirely their possible effects.[69,70] Brain volumes were different in parts of the insula in individuals with EDs or obesity in past studies, which could have affected the findings; however, we corrected for the number of activated voxels to adjust for such effects. Interoception was altered in EDs, which could have affected the perception of taste but was included as a covariate to adjust for such effects. We included the bilateral insula in the analysis and sub-regions could have shown different results, but we felt it would be important to include the entire insula in the analysis in order not to exclude important aspects of the circuitry.[59] The classification accuracy for taste solution versus no stimulation was relatively high with around 70% for all participants, but was lower for sucrose versus control solution. This could be due to contributions of general aspects of the taste stimuli such as water based solution texture and temperature, which were similar for the study stimuli. However, smaller sub-regions of the insula could have provided more refined results, thus future studies will need to investigate insula subdivisions. Classification accuracy in BN was normal; however, a larger sample size may have shown that also the BN group has lower values. Taste pleasantness and disgust also have important influence on internal response to stimuli and brain response.[71,72] In this study we aimed to avoid conditioned emotional response and we chose a highly sweet 1 molar sucrose solution and a neutral control solution as stimuli. What we did not specifically test was disgust experience. Disgust is a complex emotion that can be related to taste stimuli, but even more so comes into play in everyday situations that for instance involve social and moral values. We could not identify commonly used disgust measures in taste fMRI research but the Disgust Scale[73] is a widely used assessment tool. Its dimensions Core Disgust, Animal Reminder Disgust, and Contamination-Based Disgust can not necessarily be related to taste experience in this paradigm, but measures form this scale have been associated with for instance OCD and it is possible that measures from this scale could be predictive of eating disorder diagnosis and this in turn could be related to brain function. Disgust in fact has been associated with anterior insula activation[74] and therefore differing experience of disgust across groups could have had impact on the brain response or classification accuracy measure. This will need further investigation in the future.

In conclusion, pattern classification is relatively new to fMRI brain imaging analysis, but provides information that goes beyond strength of activation and toward understanding of neuronal patterns, which could inform about innervation and provide a more refined approach to brain function. On basis of the study results, we propose that very

basic coding mechanisms for taste quality are altered in AN and obesity. ED cognitions should therefore not be responsible for this alteration, but under- and over-weight or food deprivation and overstimulation might drive the results observed. The functional significance of these results will need further study, but normal values in individuals recovered from AN suggest that taste stimuli coding may be state dependent and recover with weight restoration.

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