

Increased anticipatory but decreased consummatory brain responses to food in sisters of Anorexia Nervosa patients

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Title:

Increased Anticipatory but Decreased Consummatory brain responses to Food
in Sisters of Anorexia Nervosa Patients.

Running Title:

Effects of familial history of anorexia nervosa on neural response to food

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Abstract

Background

We have previously shown increased anticipatory and consummatory neural responses to **rewarding and aversive food** stimuli in women recovered from anorexia nervosa (AN).

Aims

To determine if these differences are trait markers for anorexia nervosa we examined the neural response in those with a familial history but no personal history of AN.

Method

36 volunteers were recruited, 15 who had a sister with anorexia nervosa (FH) and 21 control participants. Using fMRI we examined the neural response during an anticipatory phase (**food cues, rewarding and aversive**), an effort phase and a consummatory phase (**rewarding and aversive tastes**).

Results

FH volunteers showed *increased activity in the caudate during the anticipation of both reward and aversive food and in the thalamus and amygdala during anticipation of aversive only*. FH had *decreased* activity in the dorsal anterior cingulate cortex, the pallidum and the superior frontal gyrus during taste consumption.

Conclusions

Increased neural anticipatory but decreased consummatory responses to food might be a biomarker for AN. Interventions that could normalize these differences may help to prevent disorder onset.

Introduction

Anorexia nervosa (AN) tends to affect adolescents and young women and is characterized by restricted eating and emaciation (DSM-V). The aetiology of AN is still unclear (1). However, recent research suggests abnormalities in reward and executive control as potential underlying biological mechanisms in the pathogenesis of AN (1).

Neural correlates of reward processing in individuals suffering from AN seem to be particularly interesting, especially responses to food rewards. **A recent review by Zhu et al. (2012) on fMRI studies concluded that emotional arousal (especially disgust) reflected by hyperactivation in e.g. the amygdala, the anterior cingulate cortex (ACC) and the caudate nucleus plays an important role in the processing of food information in AN (2). This is in line with the concept of increased food cue reactivity in AN patients (3, 4).** Hypoactivity in somato-sensory regions suggests reduced physical stimulation by food in patients (2). The majority of studies, however, involve visual presentation of pictorial food stimuli; neural correlates of taste processing are less common in AN.

During the application of sucrose or water, recovered AN patients have been found to have less neural activation in the insula and ventral striatum to both conditions compared to controls, which was interpreted as less pronounced reward reactions in those recovered from AN (5). Further when exposed to a pleasant chocolate drink during both hunger and satiety it was found that AN patients had increased responses in the hunger condition in the right amygdala and left medial temporal gyrus, and in the inferior temporal gyrus (extrastriate body area) in the satiety condition compared to controls (6). The authors report that this could reflect fear of weight gain and a mental focus on the body in AN patients. In a more recent study using a reward-conditioning task, which has been associated with brain dopamine reward circuits, currently ill AN patients showed increased responses in the anteroventral striatum, insula and prefrontal cortex compared to the opposite response in an obese group. Together this research points to **aberrant** brain reward activity in AN and blunted reward responses in obesity (7).

We have developed a paradigm involving the sight and taste of food stimuli which enables us to look at two aspects of food responses: anticipatory and consummatory. The former is reflecting the

concept of “wanting” and the latter the concept of “liking” (8, 9). Affective neuroscience studies of “wanting” and “liking” have suggested that these psychological processes map onto distinct brain reward systems. For example, studies of pleasure identify hedonic impact in the ventral pallidum, nucleus accumbens and orbitofrontal cortex (10-13), whereas “wanting” or incentive salience is mediated by neural systems that include mesolimbic dopamine projections from the ventral tegmental area to the ventral striatum (14). Further, dopamine has been shown to be involved in the learning about rewards in prefrontal cortical regions such as the anterior cingulate cortex and the orbitofrontal cortex (15).

Using our paradigm we have previously shown that females recovered from AN have *increased* neural responses to the anticipation of food in the occipital cortex, ACC and caudate and increased ventral striatum, insula and putamen activity to its consummation, compared to controls. As these are areas known to be involved in the processing of anticipatory and consummatory responses to rewarding stimuli in general and taste stimuli specifically, we suggested that our results might reflect a neural biomarker of risk for anorexia nervosa (16). However, as periods of malnutrition could lead to changes in the brain including microstructural alterations (17) our results may have been a consequence of recurrent AN rather than a cause. One way to resolve this issue is to study the neural response in people at increased risk of AN before the onset of illness. One reliable risk factor for AN is family heritance with genetic heritability accounting for 50 to 80% of the risk of developing an ED (18). In a large controlled family study 3.4% of female family members of women with AN had developed AN themselves (19). AN was four times more common in siblings of AN patients compared with siblings of control participants of a nation-wide register-based Danish study (20).

The present study therefore aimed to examine the neural response to food in those with a familial history of anorexia nervosa (FH) but with no personal history, compared to those with no FH, to determine if anticipatory and/or consummatory neural responses are possible trait markers for anorexia nervosa and not simply scars of starvation. Knowing whether anticipatory and/or consummatory responses to food stimuli are dysfunctional in those at risk of AN can help inform the development of psychological and pharmacological treatments that can directly target either both or

one of the processes separately. **Further we include both rewarding and aversive food stimuli to assess if any aberrant neural responses to food in the FH group is valence specific.**

We hypothesized that the FH group would have increased neural responses during both anticipatory and consummatory phases in areas such as the anterior cingulate, orbitofrontal cortex, and striatum similar to what was found in our study with those recovered from anorexia nervosa and confirming that the neural response to food might be a biomarker for risk of AN.

Methods and Materials

Participants

Fifteen women whose sisters met the DSM criteria for Anorexia Nervosa and twenty-one control subjects were recruited for this study. **Participants were recruited through advertisements both in the University and on social media sites asking “Do you have a sister with anorexia nervosa?”.** Ethics approval for the study was obtained from the Research Ethics Committee at the University of Reading. Written consent was obtained for all participants.

All participants underwent a screening process that involved a brief e-mail screening checking **that they had a sister with anorexia nervosa. Sisters then completed the Eating Disorder Diagnostic Scale (EDDS) standardized questionnaire (21). We included participants where a diagnosis of clinical anorexia nervosa had been made by a general practitioner and/or psychiatrist and the symptoms described met criteria for anorexia nervosa. We did not attempt to assess the possible presence of other Axis I or II disorders in AN sisters.** Study participants had a face-to-face assessment using the Structured Clinical Interview for DSM-IV. All participants rated the following questionnaires: the Beck Depression Inventory-2nd Edition, the Fawcett-Clarke Pleasure Scale (FCPS), the Snaith-Hamilton Pleasure Scale (SHAPS), the Rumination Questionnaire, the Ruminative Response Scale for Eating Disorders and the Eating Attitudes Questionnaire approximately 1 week before scanning. The participants completed a chocolate questionnaire to measure liking, craving, and frequency of eating chocolate (16). Current body mass index (BMI) was also recorded for each participant. Furthermore, IQ was tested using the NART (National Adult Reading Test). Inclusion criteria for all participants included 1) BMI between 18.5 and 25 kg/m², 2) maintenance of a weight in the healthy range (defined by the World Health Organisation) since menarche, 3) no use of psychoactive medications in the previous 12 months, 4) no lifetime history of any Axis 1 psychiatric disorder on the Structured Clinical Interview for DSM-IV. Participants in the control group had no first-degree relative with a current or past eating disorder diagnosis. General exclusion criteria for all participants included a history of head injury, neurological or other severe medical illness, pregnancy, and any contradictions

to MRI. All participants were fluent in English, right-handed, had normal or corrected to normal vision, and were not taking medication except for the contraceptive pill. **On the scan day participants completed a Visual Analogue Scale (VAS) measuring mood related items including happiness, anxiety and disgust, they also completed the mood questionnaire Befindlichkeits Scale (BFS). Participants were also asked to refrain from eating chocolate for 24 hours prior to being scanned, which was checked verbally before testing. Finally participants were also asked to rate how hungry they were immediately before scanning on a VAS between 1 and 10 (Table S2).**

The task was adapted from our previous study (22) and similar to our recent study (23). It consisted of 40 trials and had 4 conditions based on the trial type (**reward or aversive**) and its level of difficulty (easy/hard). Trial type was cued by a visual stimulus (2 sec-anticipatory) which indicated either to work to win the chocolate taste or to avoid the aversive taste. Difficulty was determined by the amount of effort required to complete the effort stage (easy = 24, hard = 45 button presses). This required volunteers to press a button as fast as possible (< 6 sec) to move a bar towards the pleasant picture (reward) or away from the unpleasant picture (aversive), allowing enough time to complete easy trials but not hard. **If on reward trials volunteers were successful they received the chocolate taste (5 sec delivery –consummatory phase then 2 sec swallow cue) and if not they received the tasteless solution. If on aversive trials volunteers were successful they received the tasteless solution and if not they received the unpleasant taste (consummatory phase).** A grey image (2 sec) was presented at the end of each trial as a control for the cues. Each condition was repeated 10 times, chosen by random permutation. To sustain motivation, 4 trials (2 reward/2 aversive) were longer at 9 sec each. Volunteers also rated ‘wanting’ and ‘pleasantness’ (+2 to –2) on a Visual Analogue Scale (Figure S1).

Stimuli

For the anticipation phase we used either a picture of liquid chocolate (reward) or of a moldy drink (aversive). The rewarding taste was a Belgian chocolate drink and the aversive taste was a combination of the chocolate drink mixed with beetroot juice, providing a similar texture and caloric content but that was rated as unpleasant in valence. A tasteless solution (25×10^{-3} mol/L KCL and

2.5x10⁻³mol/L NaHCO₃ in distilled H₂O) was used as a rinse between trials. This was subtracted from the effects of the other taste stimuli to allow somatosensory and mouth movement effects to be removed (22). A picture of a grey box was presented at the end of each trial to use as a control visual stimulus. Solutions were delivered through three Teflon tubes held together by a plastic mouthpiece and connected by a one-way syringe-activated check valve (Model 14044-5, World Precision Instruments, Inc.), allowing 0.5 mL of solution to be manually delivered.

fMRI Scan

The experimental protocol consisted of an event-related interleaved design. A Siemens Magnetom Trio 3T whole body MRI scanner and a 12-channel head coil were used at the Centre for Integrative Neuroscience and Neurodynamics at the University of Reading. 3T-weighted echo planar imaging slices were acquired every 2 sec (repetition time 2 sec). 36 axial slices with in-plane resolution of 3x3mm and between-plane spacing of 3mm were obtained. The matrix size was 64x64, and the field of view was 192x192mm. Acquisition was carried out during the task performance yielding, on average, 1130 volumes in total. A whole-brain 3T-weighted echo planar imaging volume of the above dimensions and an anatomic T1 volume with axial plane slice thickness of 1 mm and in-plane resolution of 1x1mm were also acquired.

fMRI analysis

Statistical Parametric Mapping (SPM8: <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) was used to analyze the imaging data as documented in our previous study (16). Data was pre-processed using realignment, normalization to the Montreal Neurological Institute (MNI) coordinate system and spatial smoothing with a 6-mm full-width-at-half-maximum Gaussian kernel and global scaling. The time series at each voxel was low-pass filtered with a hemodynamic response kernel. Time series non-sphericity at each voxel was estimated and corrected for, and a high-pass filter with a cut-off period of 128 sec was applied.

In the single-event design, a general linear model was then applied to the time course of activation in which stimulus onsets were modelled as single impulse response functions and then convolved with the canonical hemodynamic response function. Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation, linear contrasts of parameter estimates were defined to test **the specific effects of the 4 conditions (pleasant cue – grey image, unpleasant cue – grey image, pleasant taste-rinse, unpleasant taste – rinse)** with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding t statistic, which was then transformed into the unit normal distribution (SPM z). Movement parameters for each person were added as additional regressors in the 1st level analyses.

Second-level fMRI analyses first examined simple main effects of task with one-sample t -tests for all scans (Table S1). These results were thresholded at $p=0.05$ uncorrected and whole-brain cluster corrected [$p<0.05$ family-wise error (FWE) for multiple comparisons]. To examine the effect of group, independent T-Tests were implemented in SPM8 **for each of the 4 conditions separately** and all data were reported thresholded at $p=0.05$ uncorrected and **whole-brain cluster corrected ($p<0.05$ Family Wise Error for multiple comparisons)**. Plots of contrast estimates were extracted using the plots tool in SPM8, and WFU Pick Atlas (<http://www.fmri.wfubmc.edu/cms/software>) was used to display neural activation, with error bars representing the standard error of the mean. Activation co-ordinates are listed in the stereotactic space of the MNI ICBM 152 brain (Table 2).

Results

Participant Characteristics

The two groups were matched for age, BMI, and chocolate eating/liking (Table 1). There were significant differences between the control group and the FH group in the measures of anhedonia (Snaith–Hamilton Pleasure Scale, [$F(31)=1.182$, $p<.05$], Fawcett-Clarke Pleasure Scale, [$F(31)=1.914$, $p<.05$]). There were no significant differences between groups on measures of depression (Beck Depression Inventory), attitudes to eating (Eating attitudes tests), pleasure (Temporal Experience of

Pleasure Scale), motivation (Behavioural Activation Scale-Behavioural Inhibition Scale) or rumination (Ruminative Response Scale for Eating Disorders, Rumination Questionnaire) (Table 1). On the day of the scan, there were no significant differences between groups on the Visual Analogue, the Befindlichkeits Scale and on subjective ratings of hunger (see Table S1).

Ratings of Stimuli

Wanting

A repeated measures ANOVA with one factor; condition with two levels (chocolate/aversive), was used to analyse group (FH and Controls) wanting of stimuli. As expected there was a significant main effect of condition on wanting ratings [$F(1,70)=1839.260$, $p<.001$], with all participants wanting the chocolate significantly more than the aversive stimuli [$t(71)=40.725$, $p<.001$]. The ANOVA revealed a significant interaction between condition and group on participants wanting ratings [$F(1,70)=13.298$, $p=.001$]. T-tests revealed that controls wanted the chocolate significantly more than the FH group [$t(70)=2.636$, $p=.01$], the control group also wanted the aversive stimuli significantly less than the FH group [$t(70)=-2.382$, $p<.05$] (Fig S2).

Liking

To analyse the groups (FH and Controls) liking of the stimuli, a repeated measures ANOVA with one factor; condition with three levels (**chocolate, tasteless rinse and aversive**), was used. As expected, there was a significant main effect of condition on all participants liking ratings [$F(2,68)=172.295$, $p<.001$] with all participants liking the chocolate significantly more than the rinse [$t(106)=11.10$, $p<.001$] and the aversive stimuli [$t(70)=19.528$, $p<.001$]. Despite no significant interaction between condition and group [$F(2,68)=2.682$, $p=.076$], post-hoc t-tests revealed that the

control group liked the chocolate stimuli significantly more than the FH group [$t(34)=2.028$, $p=.05$] (Fig S2). There were no group differences in participants liking of tasteless rinse [$t(70)=-1.761$, $p=.083$] or of the aversive stimuli [$t(34)=-1.405$, $p=.169$].

Button Presses to complete reward effort phase.

Repeated measures ANOVAs with two factors; difficulty (easy and hard) and group (FH and Controls) were used to analyse button presses on the chocolate trials. There was a significant main effect of difficulty on participants number of button presses [$F(1,34) = 166$, $p<.001$], with all participants pressing more on hard chocolate trials (Fig S3a). There was also a significant interaction between difficulty and group [$F(1,34) = 14.98$, $p<.001$], with the controls pressing more than FH for the hard chocolate trials [$t(34) = 3.449$, $p=0.002$].

Button Presses to complete aversive effort phase.

Repeated measures ANOVAs with two factors; difficulty (easy and hard) and group (FH and Controls) were used to analyse button presses on the aversive trials. There was a significant main effect of difficulty on participants number of button presses [$F(1,34) = 167$, $p<.001$], with all participants pressing more on hard chocolate trials (Fig S3b). There was also a main effect of group [$F(1,34) = 10.7$, $p=.002$] and significant interaction between difficulty and group [$F(1,34) = 10.6$, $p=.003$], with the controls pressing more than FH for the hard aversive trials [$t(34) = 3.275$, $p=0.002$].

Time taken to complete reward effort phase.

Repeated measures ANOVAs with two factors; difficulty (easy and hard) and group (FH and Controls) were used to analyse time taken on the chocolate trials. There was a significant main effect of difficulty on participants number of button presses [$F(1,34) = 368$, $p<.001$], with all participants being faster on chocolate easy trials (Fig S4a). There was also a main effect of group [$F(1,34) = 16.4$, $p<.001$] and significant interaction between difficulty and group [$F(1,34) = 14.8$,

$p < .001$], with the FH taking longer than the controls on the chocolate easy trials [$t(34) = -3.98$, $p < 0.001$] and hard trials [$t(34) = -3.67$, $p < 0.001$] (Fig S4a).

Time taken to complete aversive effort phase.

Repeated measures ANOVAs with two factors; difficulty (easy and hard) and group (FH and Controls) were used to analyse time taken on the aversive trials. There was a significant main effect of difficulty on participants number of button presses [$F(1,34) = 334$, $p < .001$], with all participants being faster on aversive easy trials (Fig S4b). There was also a main effect of group [$F(1,34) = 10.66$, $p = 0.003$] and significant interaction between difficulty and group [$F(1,34) = 10.38$, $p = .003$], with the FH taking longer than the controls on the aversive easy trials [$t(34) = -3.26$, $p = 0.003$] and hard trials [$t(34) = -2.75$, $p = 0.009$] (Fig S4b).

Accuracy

It was expected that easy trials would be successfully completed and participants would achieve the chocolate taste and on aversive easy trials avoid the aversive taste and instead receive the tasteless rinse. It was also expected that the hard trials wouldn't be completed and participants would fail to achieve the chocolate and instead receive the tasteless rinse on chocolate trials and fail to avoid the aversive taste on hard aversive trials. Therefore, an error here means that participants did not perform as expected. Using independent samples t-tests we found that the FH group made more errors for both the chocolate easy trials [$t(34) = 1.221$, $P < 0.001$] and the aversive easy trials [$t(34) = 10.437$, $p < 0.05$] compared to the controls (Fig S5).

fMRI Response

Main Effects of Task

Table S2 provides a summary of the results for each contrast across all participants to indicate the main effect of task. Sights of the food stimuli (anticipation phase) activated regions including the occipital cortex, the ACC and lateral orbitofrontal cortex. As expected, the tastes activated areas such as the insula and ventral striatum (see Table S2).

Main Effects of Group

Table 2 provides a summary of the results of the interaction with group (FH vs. control). As expected, there was no significant differences in response to the taste of chocolate between the two groups in the primary taste cortex (i.e., anterior insula), confirming that the sensory experience of chocolate was associated with a similar neural response across groups (Table 2). As participants showed significant differences in measures of anhedonia (FCPS and SHAPS), and these measures were shown to be highly correlated $r=-.492$, $p<.01$, SHAPS scores were therefore entered as a covariate into the fMRI analysis. With only two exceptions, the fMRI results remained significant after global SHAPS scores were added as a covariate.

Anticipation:

In support of our previous findings with recovered AN we found increased activation during the anticipation phase (chocolate pictures and aversive pictures) in the FH group compared with the control group in the planum polare/amygdala region (Figure 1) and the caudate/thalamus region (Figure S4) (Table 2).

Consummation:

However we found reduced activation in the FH group compared with the control group for the unpleasant taste, in the pallidum/putamen region (Figure 2; Table 2) the superior frontal gyrus (SFG) the dorsal anterior cingulate cortex (dACC) (Figure S5). We found no differences between the groups for the chocolate taste.

Discussion

In this study we examined the neural response during the anticipation and consummation of **rewarding and aversive food** stimuli in those with a family history (FH) of AN, by virtue of having a sister with AN, compared to controls with no family history. **We found that there were increased activations to the anticipation of both rewarding and aversive food but decreased responses to the consummation of aversive food.**

Specifically we found that the FH group had increased caudate, thalamus and amygdala activations to the anticipation of both pleasant and unpleasant food. **These results are consistent with our previous study which found that females with a personal history of AN also had increased neural responses during the anticipation of food (16).** As discussed in a recent review by Zhu et al., examining mostly visual food stimuli in AN, increased activation such as this could be related to increased emotional arousal in response to food (2). Brain regions such as the caudate are thought to be involved in valence and salience coding of rewards, and have been found more active in weight-concerned women when choosing high energy food from a selection of pictures (25) and in a meta-analysis of studies on food cue processing in AN patients suggested to be coding the emotion of disgust (2). **Therefore our result of increased activity in these regions during anticipation of food might suggest a mechanism for increased negative emotional reactions in those at risk of eating disorders.** In fact consistent with this notion the FH group reported wanting the food less after seeing the cue than did the control participants supporting a negative emotional response during the anticipatory phase, **however further exploratory correlational analysis did not find any relationship in the FH or control group between brain responses in the amygdala and liking or wanting ratings for the aversive taste and cue. This may be due to both the volunteers being healthy and a small sample size.**

The increased amygdala response in our study during the anticipation phase of the unpleasant cue in the FH group, compared to the controls, might be due to increased disgust as amygdala activation has been found to correlate with disgust ratings in AN patients when confronted with food stimuli (26) and is known to be activated by aversive stimuli from multiple sensory modalities (27). Taken together, our results show that even in those “at risk” of AN but with no current symptoms or history of starvation

there are hyper-activations to the anticipation of food, supporting the idea that AN subjects may be highly responsive to food cues, perhaps as a mechanism to predict and control the anxiety produced by food that may be associated with subjective unpleasantness (28,29).

Interestingly during the consummation phase of the task we found *reduced* neural responses in the FH group compared to the control group specifically for the unpleasant taste and in the dACC, pallidum/putamen and superior frontal gyrus (SFG). The ACC has been implicated in the coding of sensory-hedonic responses to taste and innervates the striatum, where behavioral responses are then computed (28). Thus reduced activity in this region in the FH group might indicate a mechanism by which there is a vulnerability towards reduced liking of food in AN, this was also supported by the behavioural responses of reduced liking for the chocolate in the FH group. Further as the SFG is involved in self-awareness and rumination in eating disorders (30, 31) and the pallidum has been identified as a “hedonic hotspot” with a pivotal role for food liking in the brain (9) it seems that diminished responses in these regions in the FH group could explain a mechanistic predisposition towards reduced pleasure from food tastes.

As no differences between the FH group and controls were found in the activations of the primary taste cortex (anterior insula) our results are unlikely to be related to differences in physical sensitivity to taste and oral texture between the groups. **Interestingly, in our previous study in those “at risk” of anorexia namely recovered anorexia nervosa patients, we found similar regions activated to the aversive taste such as the putamen and dACC. However unlike the previous study of increased responses in those recovered we find decreased response in the FH group. Therefore we suggest that decreased activity in these regions to the unpleasant tastes is more like a trait marker which might only switch to hypersensitivity (increased activation) after experiencing anorexia nervosa (state) and is perhaps modulated by the amount of starvation experienced. Further studies longitudinal in nature are of course needed to clarify this.**

Taken together our results suggest that the neural response during anticipatory and consummatory responses to rewarding and aversive food stimuli might be a biomarker for risk of developing anorexia nervosa in the future. Therefore interventions with those at risk of AN that can normalise these differences in brain activity may be helpful in preventing the disorder onset. To clarify this, longitudinal studies investigating the neurobiological profiles of adolescents and young women at risk of AN are needed.

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Table 1. Group Demographics and Psychosocial Measures

Measure	Group			
	FH (n=15)		Controls (n=21)	
	Mean	SD	Mean	SD
Age	23.71	9.43	24.06	7.37
BMI	22.37	1.94	22.10	2.44
IQ	116.6	4.16	112.5	6.74
BDI-II	4.03	4.15	4.95	4.27
FCPS	135.47	9.45	143.74	12.51 ^a
EAT	26.29	10.54	28.11	10.12
SHAPS	21.21	4.15	18.00	4.48 ^a
TEPS	85.50	8.62	87.74	9.30
RRS-ED	11.21	3.21	11.11	2.45
RSTQ	82.00	20.54	78.16	21.85
BIS-BAS	51.00	4.95	46.82	5.99
Chocolate				
Craving	5.69	2.32	6.42	2.36
Liking	7.46	1.76	7.68	2.31

BMI, body mass index; BDI-II, Beck Depression Inventory—2nd Edition; FCPS, Fawcett–Clarke Pleasure Scale; EAT, Eating Attitudes Test; SHAPS, Snaith–Hamilton Pleasure Scale; TEPS, Temporal Experience of Pleasure Scale; RRS-ED, Ruminative Response Scale for Eating Disorders; RSTQ, Rumination State Test Questionnaire; BIS-BAS, Behavioural Inhibition System/Behavioural Approach System; VAS, Visual Analogue Scale.

^a $p < 0.05$ Independent Samples T-Test

Table 2. Group differences in neural responses to reward and aversion.

<i>Brain Region</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z score</i>	<i>P value</i>
Anticipatory					
Chocolate Cue: FH > Controls					
Caudate	4	-6	6	3.43	0.004
Unpleasant Cue: FH > Controls					
Planum polare/amygdala	40	-6	-20	3.44	<0.001
Caudate	4	-6	6	3.36	<0.001
Thalamus	-2	-10	10	3.37	0.005
Consummatory					
Unpleasant taste: Controls > FH					
Superior Frontal Gyrus	16	32	62	3.11	0.02
Pallidum/putamen	20	-2	6	2.86	0.02
dACC	10	4	28	2.96	0.02 ^a

Coordinates are defined in the Montreal Neurological Institute (MNI) stereotactic space.
p values whole brain fully corrected at the cluster level (FWE $p < 0.05$ **Family Wise Error for multiple comparisons**).

^a $p > .05$ with SHAPS as a covariate

Legends:

Figure 1: Unpleasant cue: **(A)** Axial, sagittal and coronal image of increased amygdala activation in FH vs. C group. **(B)** Contrast estimates centred at -30, -2, -20 (amygdala) in FH and C groups.

Figure 2: Unpleasant taste: **(A)** Axial, sagittal and coronal image of decreased pallidum activation in FH vs. C group. **(B)** Contrast estimates centred at 20, -2, 6 (pallidum) in FH and C groups.

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