Increased Neural Processing of Rewarding and Aversive Food Stimuli in Recovered Anorexia Nervosa

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Background: Recent evidence has shown that individuals with acute anorexia nervosa and those recovered have aberrant physiological responses to rewarding stimuli. We hypothesized that women recovered from anorexia nervosa would show aberrant neural responses to both rewarding and aversive disorder-relevant stimuli.

Methods: Using functional magnetic resonance imaging (fMRI), the neural response to the sight and flavor of chocolate, and their combination, in 15 women recovered from restricting-type anorexia nervosa and 16 healthy control subjects matched for age and body mass index was investigated. The neural response to a control aversive condition, consisting of the sight of moldy strawberries and a corresponding unpleasant taste, was also measured. Participants simultaneously recorded subjective ratings of "pleasantness," "intensity," and "wanting."

Results: Despite no differences between the groups in subjective ratings, individuals recovered from anorexia nervosa showed increased neural response to the pleasant chocolate taste in the ventral striatum and pleasant chocolate sight in the occipital cortex. The recovered participants also showed increased neural response to the aversive strawberry taste in the insula and putamen and to the aversive strawberry sight in the anterior cingulate cortex and caudate.

Conclusions: Individuals recovered from anorexia nervosa have increased neural responses to both rewarding and aversive food stimuli. These findings suggest that even after recovery, women with anorexia nervosa have increased salience attribution to food stimuli. These results aid our neurobiological understanding and support the view that the neural response to reward may constitute a neural biomarker for anorexia nervosa.

Key Words: Anorexia nervosa, fMRI, insula, recovered, reward, ventral striatum

Anorexia nervosa is characterized by an intense fear of gaining weight or becoming fat and refusal to maintain a minimum healthy body weight of the expected standard for age and height (1). In addition, individuals with anorexia nervosa evaluate themselves largely in terms of their weight and shape and ability to control them (1). To date there is no clear evidence-based treatment (2), and the prognosis remains poor (3).

Recent research has highlighted potential underlying biological mechanisms in the pathogenesis of anorexia nervosa (4,5). One area of particular interest is the neural representation of reward. Studies have investigated the neural correlates of reward processing in individuals acutely ill, usually employing indirect reward stimuli such as food or body images (6–9).

However, when individuals are underweight, as in acute anorexia nervosa, cognitive and physiological systems are severely disturbed (10). It is not possible to determine whether the abnormalities in reward processing are a cause or consequence of starvation. To avoid the confounding effects of current starvation, studies have also investigated the neural representation of reward after recovery. This is also important because it is recognized that after recovery, individuals often continue to display core eating disorder symptoms (11). One functional magnetic resonance imaging (fMRI) study focused on striatal activity to monetary wins and losses in recovered anorexia nervosa (12). They found that unlike healthy control subjects, the anorexia nervosa participants failed to show an anterior ventral striatum response that distinguished between winning and losing (12). Because the ventral striatum is implicated in reward processes (13,14), it was suggested that this response may reflect a failure to differentiate the emotional significance of stimuli.

Studies have also used symptom-provoking paradigms and fMRI to delineate alterations in brain function after recovery from anorexia nervosa. Uher and colleagues (15) found increased neural responses to food stimuli in the medial prefrontal cortex and the anterior cingulate cortex in both a recovered and currently ill anorexia nervosa group compared with healthy control subjects. The medial prefrontal cortex is believed to code the emotional significance of stimuli (16), whereas the anterior cingulate cortex is implicated in reward-based decision making (17). The authors concluded that these areas appear to be functionally linked to food-related stimuli and may represent a trait vulnerability of anorexia nervosa (15). Alternatively, it is possible that these findings may represent a scar of the illness.

Similarly, Wagner and colleagues examined the effects of gustatory stimulation on brain activity in recovered anorexia nervosa (10). They provided initial evidence that individuals who have recovered from anorexia nervosa display lower neural activation after sucrose, a pleasant taste, and water administration in the insula, including the primary cortical taste region, and in the ventral and dorsal striatum compared with healthy control subjects. The authors suggest that individuals with anorexia nervosa process taste stimuli differently from healthy control subjects (10).

We have developed an experimental paradigm that allows study of the neural responses to primary and secondary rewarding and aversive stimuli in the human brain using fMRI (18–21). The aim of this study was to examine the neural response in individuals recovered from anorexia nervosa compared with healthy control subjects to rewarding and aversive unconditioned stimuli. We hypothesized that individuals recovered from anorexia nervosa would have aberrant neural responses to the sight and taste of

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pleasant chocolate and aversive strawberry stimuli in the brain regions that have been shown to be activated by this task, such as the ventral striatum, caudate, insula, medial prefrontal, and orbitofrontal cortices (18–21).

Methods and Materials

Participants

Fifteen women who had previously met DSM criteria (1) for anorexia nervosa and sixteen healthy control subjects were recruited for this study. Participants were recruited through advertisements. Ethical approval for the study was obtained from the University of Oxford and Outer West London Research Ethics Committee. Written informed consent was obtained for all participants.

All participants underwent a screening process that involved a brief e-mail screening and a face-to-face assessment using the Structured Clinical Interview for DSM-IV (22). Current eating disorder symptoms in all participants were assessed using the Eating Disorder Examination Questionnaire (EDE-Q) (23). All participants also rated the following questionnaires: the Beck Depression Inventory—2nd Edition (24), the Fawcett–Clarke Pleasure Scale (25), the Snaith–Hamilton Pleasure Scale (26), and the Trait Anxiety Inventory (27) approximately 1 week before scanning. The participants also completed a chocolate questionnaire to measure liking, craving, and frequency of eating chocolate (19). Current body mass index (BMI), lowest ever BMI, duration of illness, and length of recovery was also recorded for the recovered anorexia nervosa group.

Criteria for inclusion in the recovered group included 1) a history of DSM-IV anorexia nervosa (1), 2) maintenance of a BMI of between 18.5 and 25 kg/m^2 for 12 months 3) regular menstruation for 12 months, and 4) no use of psychoactive medications in the previous 12 months. In addition, recovered participants had to score within one standard deviation of the EDE-Q global mean scores for young women (28). The 15 recovered individuals had met criteria for restricting-type anorexia nervosa. In addition, four recovered participants had met criteria for bulimia nervosa and one for an eating disorder not otherwise specified during their lifetime. Nine of the recovered participants had fulfilled the criteria for major depressive disorder and three for obsessive-compulsive disorder during their lifetime.

Inclusion criteria for the healthy control group were 1) BMI between 18.5 and 25 kg/m^2, 2) no first-degree relative with a current or past eating disorder diagnosis, 3) no lifetime history of any Axis 1 psychiatric disorder on the Structured Clinical Interview for DSM-IV (22), and 4) maintenance of a weight in the healthy range (defined by the World Health Organization) since menarche.

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.

Stimuli

Stimuli were delivered to the subject's mouth through three Teflon tubes (for the tasteless rinse, the chocolate taste and the strawberry taste); the tubes were held between the lips. Each tube was connected to a separate reservoir via a syringe, and a one-way syringe activated check valve (Model 14044-5; World Precision Instruments, Stevenage, United Kingdom), which allowed .5 mL of any stimulus to be delivered manually at the time indicated by the computer. The chocolate was formulated to be liquid at room temperature (whole milk, chocolate powder, cocoa, sugar, milk powder). A control tasteless solution .5 mL of a salivalike rinse solution (25×10^{-3} mol/L KCl and 2.5×10^{-3} mol/L $NaHCO_3$ in distilled H_20) was used between trials (described in Table S1 in Supplement 1), and when subtracted from the effects of the other stimuli, it allowed somatosensory and any mouth movement effects to be subtracted from the effects produced by the other oral stimuli (29,30). This allows the taste, texture, and olfactory areas to be shown independently of any somatosensory effects produced by introducing a fluid into the mouth (20,29–32). The aversive stimulus was a strawberry drink (glycol, glycerol, mannitol, hydrobenzoate; Rosemont Pharmaceuticals, Leeds, United Kingdom) that was rated as intense as the chocolate but unpleasant in valence (20). Both the liquid chocolate and the strawberry had approximately the same sweetness and texture, which enabled them to pass freely through the tubes.

Experimental Procedure

At the beginning of each trial, one of the six stimuli chosen by random permutation was presented. If the trial involved an oral stimulus, this was delivered in a .5 mL aliquot to the subject's mouth. At the same time, a visual stimulus was presented, which was a picture of chocolate, moldy strawberries, or a gray control image. The image was turned off after 7 sec, at which time a green cross appeared on a visual display to indicate to the subject to swallow. After a delay of 2 seconds, the subject was asked to rate each of the stimuli for "pleasantness" (with +2 being *very pleasant* and –2 *very unpleasant*), for "intensity" (0 to +4), and for "wanting" (+2 for *wanting very much*, 0 for *neutral*, and –2 for *very much not wanting*). The ratings were made with a visual analog scale in which the subject moved a bar using a button box. After the last rating, the gray visual stimulus indicated the delivery of the tasteless control solution, which was also used as a rinse between stimuli; this was administered in the same way as a test stimulus. The tasteless control was always accompanied by the gray visual stimulus. On trials in which only the picture of chocolate was shown, there was no rinse, but the gray visual stimulus was shown to allow an appropriate contrast to be made. There was then a 2-sec delay period that allowed for swallowing, followed by a 1-sec gap until the start of the next trial. A trial was repeated for each of the six stimulus conditions shown in Table S1 in Supplement 1, and the cycle was repeated nine times. The instruction given (on taste trials) was to move the tongue once as soon as a stimulus or tasteless solution was delivered to distribute the solution to activate the receptors for taste and smell. Subjects were then instructed to keep still for the remainder of the 7-sec period until the green cross was shown, at which point they could swallow. This procedure has been shown to allow taste effects to be demonstrated clearly with fMRI, using the procedure of subtracting any activations produced by the tasteless control from those produced by a taste or other stimulus (29–32).

fMRI Scan

The experimental protocol consisted of an event-related interleaved design. fMRI of the brain was performed with a Siemens Avanto 1.5-T whole-body scanner at the Oxford Centre for Magnetic Resonance Imaging. T2*-weighted echo planar imaging slices were acquired every 2 sec (repetition time = 2). Axial slices with in-plane resolution of 3 × 3 mm and between-plane spacing of 3 mm were obtained. The matrix size was 64 × 64, and the field of view was 192 × 192 mm. Acquisition was carried out during the task performance yielding 972 volumes in total. A whole-brain T2*-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 1 × 1mm were also acquired.

Table 1. Group Demographic and Psychosocial Measures

	Group			
	Recovered Anorexia Nervosa ($n = 15$)		Healthy Control ($n = 16$)	
Measure	Mean	SD	Mean	SD
Age	23.33	3.50	24.10	2.90
BMI	21.33	2.17	21.19	1.56
IQ	115.94	4.66	113.30	4.24
EDE-Q	1.11	1.13	.33	.46[a]
BDI-II	5.87	6.81	2.25	2.54
TAI	16.47	10.27	13.27	8.50
FCPS	134.53	10.90	135.31	20.27
SHAPS	21.4	5.08	19.13	4.62
Chocolate				
Craving	5.13	2.53	6.56	1.46
Liking	7.27	2.05	8.06	1.39
Frequency of Eating	3.38	2.41	2.51	1.66
Lowest BMI (kg/m^2)	14.27	1.94	—	—
Age of Anorexia Nervosa Onset	14.73	1.94	—	—
Length of Recovery (months)	42	28.57	—	—

BDI-II, Beck Depression Inventory—2nd Edition; BMI, body mass index; EDE-Q, Eating Disorder Examination Questionnaire; FCPS, Fawcett–Clarke Pleasure Scale; SHAPS, Snaith–Hamilton Pleasure Scale; TAI, Trait Anxiety Inventory.

[a] $p < 0.05$ Mann–Whitney *U*.

Data Analysis

The imaging data were analyzed using statistical parametric mapping software (SPM 8, Wellcome Department of Cognitive Neurology, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Pre-processing involved realignment, reslicing with sinc interpolation, normalization to the Montreal Neurological Institute coordinate system and spatial smoothing with a 6-mm full width at half maximum isotropic Gaussian kernel. Time series non-sphericity at each voxel was estimated and corrected for (33), and a high-pass filter with a cutoff 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 modeled as single impulse response functions and then convolved with the canonical hemodynamic response function (34). 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 each condition with each individual data set. 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). The statistical parametric maps from each individual data set were then entered into second-level, random-effects analyses accounting for both scan-to-scan and subject-to-subject variability. SPM converts the *t* statistics to *Z* scores. We examined simple main effects of group with one-sample *t* tests. To assess the between group differences for each condition, two-sample *t* tests were used. Corrected *p* values were based on the spatial extent of clusters of 30 or more contiguous voxels above a threshold of $p < .05$ and fully corrected for the number of comparisons (resels) in the entire brain volume ("whole-brain" multiple comparisons for which $p < .05$ family-wise error, EDE-Q scores added as a covariate of no interest). Plots of contrast estimates are extracted using the plots tool in SPM8. Coordinates of the activations are listed in the stereotactic space of the Montreal Neurological Institute's ICBM152 brain.

Results

Participant Characteristics

The two groups were matched for age, IQ, BMI, and chocolate eating/liking (Table 1). There were no differences between the control group and the recovered anorexia nervosa group in the measures of anhedonia (Snaith–Hamilton Pleasure Scale, Fawcett–Clarke Pleasure Scale), depression (Beck Depression Inventory), or anxiety (Trait Anxiety Inventory). However, the recovered group scored significantly higher on the EDE-Q (Table 1).

Ratings of Stimuli

Using a repeated-measures analysis of variance for the pleasantness, intensity, and wanting ratings, there were no significant differences between the two groups and their ratings of pleasantness over the six stimuli [$F(1,29) = 3.08$, $p = .09$], intensity over the six stimuli [$F(1,29) = .95$, $p = .34$], or wanting over the six stimuli [$F(1,29) = 2.80$, $p = .11$]. (See Table S2 in Supplement 1.)

fMRI Response

Table S3 in Supplement 1 provides a summary of the results for each contrast across all participants to indicate the main effect of task. Table 2 provides a summary of the results of the interaction with group (recovered anorexia nervosa vs. healthy control subjects). The fMRI results remained significant when global EDE-Q scores were added as a covariate.

Main Effects of Task

As expected, the taste stimuli of chocolate and strawberry activated an overlapping region of the anterior insula in both healthy control subjects and recovered anorexia nervosa participants (see Table S3 in Supplement 1). Both chocolate and strawberry picture stimuli activated bilaterally regions of the occipital cortex. The chocolate taste and chocolate picture activated areas of reward relevant circuitry, more specifically the ventral striatum and anterior cingulate cortex. In contrast, the aversive stimuli of strawberry

Table 2. Regions Showing Significant Effect of Group on Each Condition

Brain Region	MNI Coordinates x	y	z	*Z* Score	*p* Value
Chocolate in Mouth: Recovered Anorexia Nervosa > Healthy Controls					
Ventral striatum	12	8	0	4.28	<.001
Putamen	−20	2	8	4.65	<.001
Posterior cingulate	0	−36	20	4.28	<.001
Sight of Chocolate: Recovered Anorexia Nervosa > Healthy Controls					
Occipital cortex	38	−80	−10	3.66	.001
Anterior prefrontal cortex	12	66	12	3.70	.003
Subgenual cingulate/medial prefrontal cortex	−1	28	−12	3.49	.003[a]
Chocolate in Mouth with Sight of Chocolate: Recovered Anorexia Nervosa > Healthy Controls					
Pallidum	14	10	−4	2.92	.04
Strawberry in Mouth: Recovered Anorexia Nervosa > Healthy Controls					
Insula	42	−14	4	3.20	<.001
Putamen	24	4	14	3.49	<.001[a]
Strawberry in Mouth with Sight of Strawberry: Recovered Anorexia Nervosa > Healthy Controls					
Anterior cingulate cortex	10	6	34	3.8	<.001
Operculum	42	−14	20	3.74	<.001
Caudate	14	12	12	3.45	<.001
Dorsolateral prefrontal cortex	8	46	22	3.34	.004

p value clusters whole-brain fully corrected (family-wise error $p < .05$; Eating Disorder Examination Questionnaire added as covariates of no interest). Coordinates are defined in the Montreal Neurological Institute (MNI) stereotactic space.

[a] $p > .05$ after adding Eating Disorder Examination Questionnaire global scores as a covariate.

taste and the sight of moldy strawberries activated areas involved in aversive processing including lateral orbitofrontal cortex, the caudate, and insula cortex (Table S3 in Supplement 1).

Effects of Group

As expected, there was no significant difference in response to the taste of chocolate between the two groups in the primary taste cortex (i.e., anterior insula) (35), confirming that the sensory experience of chocolate was associated with a similar neural response across groups (Table 2).

Chocolate Reward: Taste and Sight

The recovered anorexia nervosa group showed increased responses to the taste of chocolate in areas known to play a key role in reward, including the ventral striatum (Figure 1) and cingulate cortex. There was also increased activation to the sight of chocolate

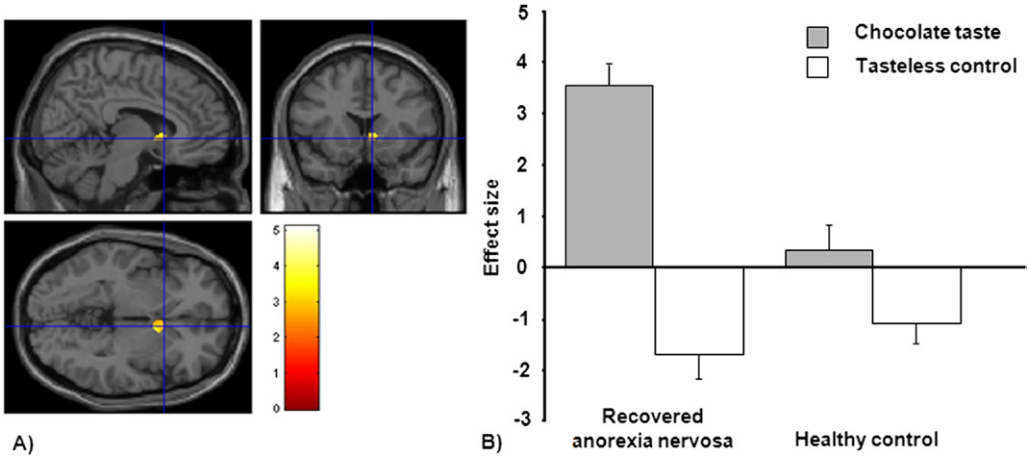

Figure 1. Chocolate in the mouth condition: recovered anorexia nervosa versus healthy control subjects. **(A)** Axial, sagittal, and coronal image of significantly increased ventral striatum activation in the recovered anorexia nervosa group compared with the healthy control group. **(B)** Contrast estimates centered at 12, 8, 0 for the recovered anorexia nervosa group compared with the healthy control group ($p < .001$).

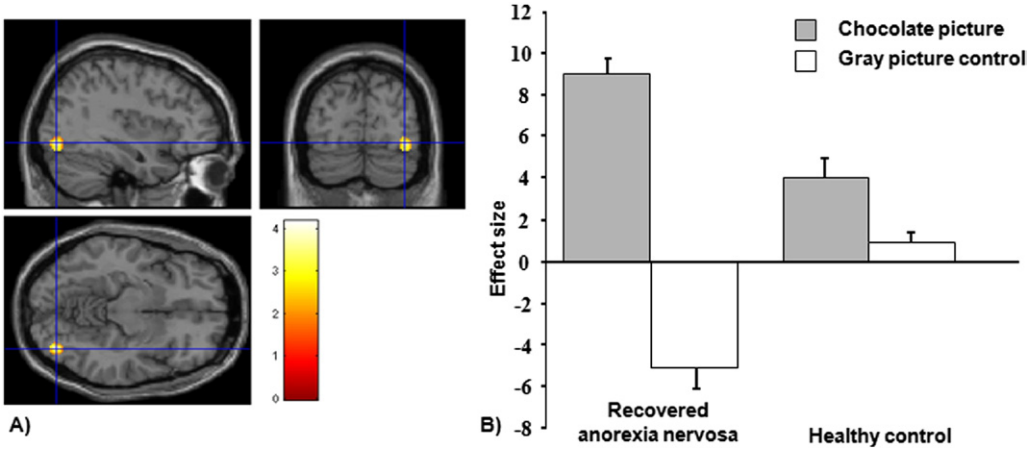

Figure 2. Sight of chocolate condition: recovered anorexia nervosa versus healthy control subjects. **(A)** Axial, sagittal, and coronal image of increased occipital activation in the recovered anorexia nervosa group compared with the healthy control group. **(B)** Contrast estimates centered at 38, −80, −10 for the recovered anorexia nervosa group compared with the healthy control group ($p = .001$).

alone in the recovered group compared with the healthy control group in the occipital cortex (Figure 2), the cingulate, and medial prefrontal cortex (Table 2). There were no areas where the healthy control subjects showed increased responses relative to the recovered anorexia nervosa group for the chocolate reward condition. After correcting for multiple comparisons, there were no significant correlations between the fMRI response in the recovered anorexia nervosa group and duration of illness, lowest ever BMI, age of onset, or length of recovery in the brain regions that demonstrated increased responses to the taste and sight of chocolate.

Strawberry: Taste and Sight

There was increased activation in the recovered anorexia nervosa group compared with the healthy control group for the unpleasant strawberry taste condition and also the unpleasant strawberry taste with the picture condition. Specifically, the anterior cingulate cortex, the lateral posterior insula, putamen, caudate and dorsolateral prefrontal cortex showed increased activation in the recovered anorexia nervosa participants. (Table 2, Figure 3). There were no significant group differences when the strawberry picture was presented alone. There were no areas where the healthy control subjects showed increased responses relative to the recovered group for the aversive strawberry condition. After correcting for multiple comparisons, there were no significant correlations between the fMRI response in the recovered anorexia nervosa group and duration of illness, lowest ever BMI, age of onset, or length of recovery in the brain regions that demonstrated increased responses to the taste and sight of strawberry.

Discussion

Our findings are the first to show that those recovered from anorexia nervosa have increased ventral striatal activity to the pleasant taste of chocolate compared with healthy control participants despite no difference in subjective experience. Furthermore, our results show that those recovered also have increased insula and caudate activity to the unpleasant conditions compared with healthy control subjects. This is consistent with recent research using food stimuli during acute anorexia nervosa (6,7,9).

Because there were no differences between the two groups in their subjective ratings or primary taste cortex activations to the stimuli, it seems unlikely that our findings are attributable to conscious processing or sensory aspects of the stimuli. Rather, these results suggest dysfunctional food salience attribution as a possible neural biomarker for anorexia nervosa, which is more sensitive than subjective report. It is also important to note that the results re-

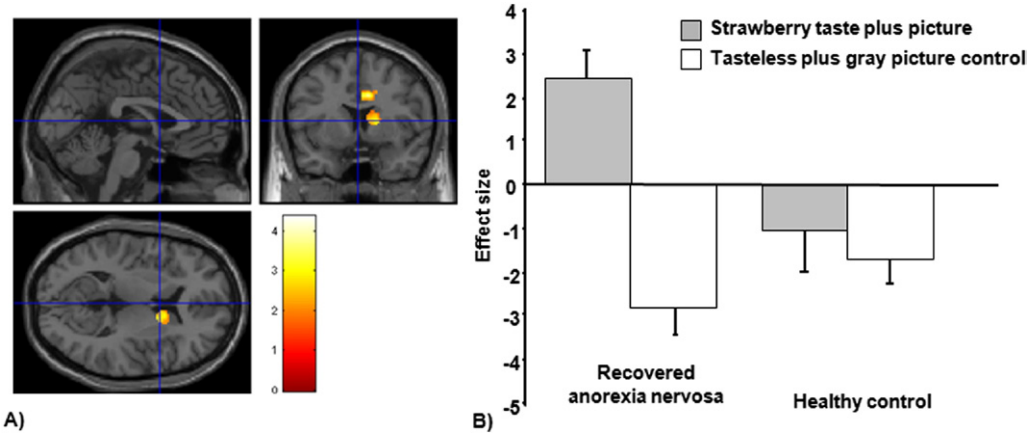

Figure 3. Strawberry in the mouth with the sight of moldy strawberry condition: recovered anorexia nervosa versus healthy control subjects. **(A)** Axial, sagittal, and coronal image of increased caudate and anterior cingulate in the recovered anorexia nervosa group compared with the healthy control group. **(B)** Contrast estimates centered at 14, 12, 12 (caudate) for the recovered anorexia nervosa group compared with the healthy control group ($p < .001$).

mained significant even after controlling for any remaining eating disorder symptoms in the recovered anorexia nervosa group. Furthermore, using the same task, we have previously found that those who are recovered from depression have *decreased* ventral striatum to reward, and therefore depression is unlikely to have related to these results (20).

The results reported here are similar to our previous study examining the neural response to chocolate in chocolate cravers (19). Like the cravers, our sample of recovered anorexia nervosa participants show increased response to chocolate in the ventral striatum but also increased neural response to the aversive food stimuli, despite no subjective differences. This supports the idea that individuals with current anorexia nervosa may have a hypersensitive neural response to food stimuli, irrespective of valence, and therefore may practice restraint to control exposure to stimuli (36).

Interestingly, studies examining the neural response to taste stimuli in obese individuals have also found increased activations in areas such as the insula, anterior cingulate, and parietal cortex (37,38). However, unlike the recovered anorexia nervosa participants, obese participants show less activation in the striatum, a brain region that contributes to the motivational salience of stimuli, in response to consumption of a chocolate drink (39). It has been suggested that obese individuals may therefore overeat to compensate for the hypofunctioning of the striatum (40,41).

Consistent with our findings, previous studies in current or past anorexia nervosa have shown increased activations to disease-specific visual stimuli, such as food pictures (6,7,9) and body figures in reward-related areas (42,43). Of note in the current study is the increased activation in the occipital cortex to the chocolate picture in the recovered group. This replicates the findings reported previously in both currently ill participants and those recovered from anorexia nervosa (7,15,44). Because occipital cortex activation has been linked to early recognition of emotional stimuli (45), it may be that anorexia nervosa reflects dysfunction in these early stages of processing.

We also found increased activation in the medial prefrontal cortex to the chocolate picture in the recovered anorexia nervosa group compared with healthy control subjects. These results are similar to that reported by Uher and colleagues (7,15). The medial prefrontal cortex subserves a variety of behaviors guided by emotional and motivational factors, including feeding (46). The increased prefrontal cortex activation to the visual chocolate stimuli may represent the need for increased top-down cognitive control in anorexia nervosa to emotionally salient cues, such as food, which may otherwise be experienced as overwhelming and aversive (4).

There have also been studies examining reward processing in anorexia nervosa that report results inconsistent with ours (10). For example, Wagner and colleagues (10) found reduced insula, ventral striatal, and anterior cingulate activations in recovered anorexia nervosa participants compared with healthy control subjects in response to a sucrose solution. It may be that compared with a sucrose solution, a chocolate drink is more salient and evokes a greater reward response. Furthermore, Wagner and colleagues used a block design with more predictable taste administrations than our current study. This may also have affected the neural response to reward. Future studies examining, for example, temporal difference errors in relation to the reward response, may be beneficial.

To our knowledge, this is the first study in recovered anorexia nervosa that has also included an aversive taste condition. The recovered group showed increased responses in the caudate nucleus and posterior insula. This is of interest because the emotion of disgust has been shown to activate both the caudate nucleus and the posterior regions of the insula (47), and this suggests that individuals recovered from anorexia nervosa show increased processing of aversive cues. This is also consistent with reports of greater sensitivity in anorexia nervosa to both punishing (48) and disgusting (49) stimuli. These results support our hypothesis that within anorexia nervosa there is a dysfunctional attribution of salience to food stimuli, whatever the valence.

Although the experience of disgust to the aversive condition may be heightened in the recovered anorexia nervosa group, we cannot exclude the possibility that the increased activation may also be linked to other negative emotions, such as anxiety (50). In line with this, eating elicits high levels of anxiety in individuals with eating disorders (4), and at the neural level, it has been shown that individuals with high levels of anxiety demonstrate heightened activation in the insula cortex to emotionally salient stimuli (51).

The dorsolateral prefrontal cortex, which also showed exaggerated activity to the strawberry taste and picture in the recovered group, is considered the highest cortical area responsible for information retrieval, motor planning, sequencing, and regulation (52). The dorsolateral prefrontal cortex is also extensively connected to a variety of brain areas including the striatum, and it has been suggested that it may modulate striatal activity that underlies the approach or avoidance of food (4). It could therefore be that the increased activation in these areas to the aversive stimuli in the recovered anorexia nervosa group represents an enhanced attempt to minimize exposure to the stimuli. This would be in line with the proposal that, even after recovery, individuals with anorexia nervosa have higher levels of harm avoidance and respond to such stimuli in a strategic way, opposed to relying on hedonic properties (4).

Group differences in anterior cingulate activation to the aversive stimuli were also found. The anterior cingulate is thought to be implicated in emotional evaluation, attentional control, and response selection (6,9,53). The increased activation reported here may therefore represent heightened selective attention for food stimuli. The anterior cingulate has also been consistently implicated in the pathogenesis of anxiety and affective disorders (54), symptoms of which are commonly present in those with anorexia nervosa (55). It may therefore be that the anterior cingulate represents part of a dysfunctional network associated with anxious and affective phenomena in a group of related disorders (7). Alternatively, it could be that the aberrant anterior cingulate activity is functionally related to a reward-punishment contamination, which has been theorized to maintain anorexia nervosa (56).

In conclusion, these findings suggest that compared with healthy control subjects, individuals recovered from anorexia nervosa show an increased neural response to both pleasant and aversive food stimuli in brain circuitry, mediating reward and aversion processing, respectively. This is despite there being no significant difference in the subjective experience of the stimuli. The results support the notion that increased attribution of salience to food stimuli may underlie anorexia nervosa and explain why self-denial and restraint, as a way of controlling and reducing exposure to the stimuli, characterizes the disorder (4,5). Studying those recovered allows the data to be unconfounded by state factors or medication, yet it is difficult to determine whether the neural dysfunction is a stable trait characteristic or a scar effect. Longitudinal studies recruiting vulnerable individuals before illness onset as well as during the acute stage are required to resolve this issue. It would also be of interest to recruit larger sample sizes to explore subtypes of anorexia nervosa and their neural response to primary rewarding and aversive stimuli.

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Supplementary material cited in this article is available online.

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