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Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa

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Abstract

Objective—Recent studies suggest that altered function of higher-order appetitive neural circuitry may contribute to restricted eating in anorexia nervosa and overeating in bulimia nervosa. This study used sweet tastes to interrogate gustatory neurocircuitry involving the anterior insula and related regions that modulate sensory-interoceptive-reward signals in response to palatable foods.

Method—Subjects recovered from anorexia and bulimia were studied to avoid confounding effects of altered nutritional state. Functional magnetic resonance imaging measured brain response to repeated tastes of sucrose and sucralose to disentangle neural processing of caloric and non-caloric sweet tastes. Whole-brain functional analysis was constrained to anatomical regions of interest.

Results—Compared to matched control women (n=14), women recovered from anorexia (n=14) had diminished ($F(1,27)=7.79$, $p=0.01$) and women recovered from bulimia (n=14) had exaggerated ($F(1,27)=6.12$, $p=0.02$) right anterior insula hemodynamic response to tastes of sucrose. Furthermore, anterior insula responses to sucrose compared to sucralose was exaggerated in recovered subjects (lower in women recovered from anorexia and higher in women recovered from bulimia).

Conclusions—The anterior insula integrates sensory/reward aspects of taste in the service of nutritional homeostasis. For example, one possibility is that restricted eating and weight loss occur in anorexia nervosa because of a failure to accurately recognize hunger signals, whereas overeating in bulimia nervosa could represent an exaggerated perception of hunger signals. This response may reflect the altered calibration of signals related to sweet taste and the caloric content of food and may offer a pathway to novel and more effective treatments.

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Introduction

Anorexia nervosa and bulimia nervosa are disorders of unknown etiology that tend to affect young women (1). They are characterized by extreme eating behavior and distorted body image, and have high rates of chronicity, morbidity, and mortality (1). Several lines of evidence implicate genetically mediated neurobiological factors as contributing to the development of anorexia nervosa and bulimia nervosa (2, 3). However, a lack of understanding of the pathophysiology of these illnesses has hindered development of effective treatments.

How are individuals with anorexia nervosa able to consume a few hundred calories per day and maintain an extremely low weight for many years, when most people struggle to lose a few pounds? And why do individuals with bulimia nervosa, who are often of normal weight, binge on thousands of calories per day? Although both are categorized as eating disorders (1), it is unknown whether individuals with anorexia nervosa and bulimia nervosa have a primary disturbance of appetite regulation or whether pathological feeding behavior is secondary to other phenomena, such as an obsessional preoccupation with body image. Recent studies of obesity suggest that corticolimbic neural processes, which encode the rewarding, emotional, and cognitive aspects of food ingestion, can drive over-consumption of food, even in the presence of satiety and replete energy stores (4, 5).

In order to determine whether corticolimbic circuits are involved in appetite regulation in eating disorders, we interrogated the neural circuitry of gustatory processing, which integrates the sensory, hedonic, and motivational aspects of feeding, following a modest meal (Figure 1) (2, 5, 6). As Small notes, this circuit can be assessed by using a sweet taste (7). Sweet taste perception is peripherally recognized by the tongue's sweet taste receptors, and these signals are transmitted through the brain stem and thalamus to the primary gustatory cortex, which is comprised of the frontal operculum and anterior insula. The anterior insula and associated gustatory cortex respond to the taste and physical properties of food and may also respond to its rewarding value. The subgenual anterior cingulate cortex is linked to hypothalamic and brainstem pathways that mediate autonomic and visceral control. The orbital frontal cortex is associated with flexible incentive responses to changing stimuli. These regions innervate a broad region of the rostral ventral-central striatum where behavioral repertoires are computed based on these inputs.

When individuals with anorexia and bulimia nervosa are in ill and symptomatic states, they have disturbances of most physiological systems. This confounds determining whether abnormal ill state findings are cause or consequence of starvation. In order to avoid confounding effects, we studied individuals recovered from restricting-type anorexia or bulimia nervosa compared to matched control women. Approximately 50% of individuals who have anorexia and bulimia nervosa recover in the sense that their weight and nutritional status normalize (8), although persistent mild to moderate dysphoric mood, obsessional thoughts, and body image concerns are common (9). Because these symptoms are present in childhood, before the onset of the eating disorder, they may reflect traits that contribute to a vulnerability to develop anorexia or bulimia.

This study used functional magnetic resonance imaging (fMRI) and sweet taste administration to interrogate top-down sensory-interoceptive-reward processes. The whole-brain functional analysis was constrained to the anatomical regions of interest based on the Talairach Atlas. We sought to replicate an earlier finding from our group (10) showing that women recovered from anorexia have reduced insula and striatal response to tastes of sucrose, which suggests diminished response of the sensory-reward circuitry responsible for

consummatory drive. Because those with bulimia have a drive to over-consume, we hypothesized they would have an exaggerated response of sensory-reward circuitry.

It is possible that the brain differentially processes sweetness compared to the caloric content of sucrose. For example, the hypothalamus responds to the caloric content of sugar (11). Thus, the non-caloric sweet solution sucralose was chosen as a contrast condition because it is similar to sugar in taste, molecular make-up, and recognition by tongue sweet receptors (12), but lacks its caloric properties (13). Disentangling processes related to sweetness versus caloric content may help understand why anorexia and bulimia nervosa subjects have strong emotional responses to high calorie foods.

Materials and Methods

Study Participants

We studied 14 women recovered from anorexia nervosa, 14 women recovered from bulimia nervosa, and compared them to 14 age- and weight-matched control women (Table 1). Trained clinicians administered the Structured Clinical Interview for DSM-IV Axis-I Disorders to assess inclusion/exclusion criteria (14) and to characterize lifetime history of comorbid psychiatric disorders (see Appendix for subject comorbidities). Subjects completed the Beck Depression Inventory (BDI (15)) to assess depression, the Temperament and Character Inventory (TCI (16)) to assess harm avoidance, and the State-Trait Anxiety Inventory-Y (STAI-Y (17)) to assess state and trait anxiety. Women recovered from anorexia had lost weight purely by restricting their diet, and had no history of binge eating or purging. Women recovered from bulimia had a history of past binge eating and purging behaviors but had never been emaciated and maintained an average body weight above 85% average body weight. No subjects had prior history of both anorexia and bulimia nervosa. Recovered subjects must have had: (a) No restrictive eating or other pathological eating related behaviors in the preceding 12 months; (b) A stable weight (±3.0kg) between 90% and 120% average body weight for at least 12months; (c) Regular menstrual cycles for the preceding 12 months; and (d) Normal plasma b-hydroxybutyric acid (BHBA), glucose, and insulin concentrations during the evaluation phase as previously described (9). Control women had no history of an eating disorder or any psychiatric or serious medical or neurological illness, no first-degree relatives with an eating disorder, and had been within normal weight range since menarche. All subjects had normal menses and were studied during the early follicular phase of the menstrual cycle. No subject took medication within 30 days prior to the study. After complete description of the study to the subjects, all participants gave written informed consent. The UCSD institutional review board approved this study.

Brain imaging procedures

Subjects were instructed to fast overnight and arrived at the fMRI facility between 7 and 8AM. Subjects received a standardized breakfast of 604 calories to control for satiety state prior to scanning.

Taste solution delivery

Sucrose and sucralose solutions were delivered with a programmable syringe pump in 1-mL per second stimulations. Subjects received 1-mL of either sugar or sucralose from a programmable pump every 20 seconds for a total of 120 samples. Sweet tastes were matched for intensity and delivered in pseudorandomized order. Additional methods, as well as other relevant issues, are described in the Appendix.

FMRI Acquisition

Imaging experiments were performed on a 3T GE Magnet, with a three-plane scout scan(16 seconds), a sagitally acquired spoiled gradient recalled(SPGR) sequence (T1-weighted, 172 slices thickness 1mm, TI=450ms, TR=8ms, TE=4ms, flip angle=12°, FOV=250x250mm, 192x256 matrix interpolated to 256x256), and T2* weighted echo-planar imaging(EPI) scans to measure BOLD functional activity during taste stimulation(3.43x3.43x2.6 mm voxels, TR=2 seconds, TE=30ms, flip angle=90°, and 32 axial slices, 2.6mm slice thickness and 1.4mm gap).

FMRI Preprocessing

Images were processed with the Analysis of Functional NeuroImages (AFNI) software. (afni.nimh.nih.gov/afni/) To minimize motion artifact, echo-planar images were realigned to the 100^{th} acquired scan. Additionally, data were time-corrected for slice acquisition order, and spikes in the hemodynamic time course were removed and replaced with an interpolated value from adjacent time points using 3dDespike. A multiple regression model was used whereby regressors derived from the experimental paradigm were convolved with a prototypical hemodynamic response function (AFNI:waver), including five nuisance regressors: three movement regressors to account for residual motion (in the roll, pitch, and yaw directions), and regressors for baseline and linear trends to account for signal drifts. To account for individual anatomical variations, a Gaussian filter with full width at half maximum 6.0mm was applied to the voxel-wise percent signal change data. All functional data were normalized to Talairach coordinates.

FMRI Analysis

Single sample t-tests were performed on the main effects of sucrose and sucralose, and statistical maps were thresholded at $p<0.005$. Both whole brain and region of interest analyses were performed. The whole brain analysis was thresholded at 2048 mm^3 (32 voxels) and masked to *a priori* regions of interest implicated in taste and reward processing (Table S1). A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false positive areas of activation.(AFNI:AlphaSim) Voxel-wise percent signal change data were entered into a group (controls/women recovered from anorexia/women recovered from bulimia) by condition (sucrose/sucralose) analysis of variance (ANOVA) test thresholded at $p<0.05$. Percent signal change data from statistically derived regions of interest were used to assess correlation and regression analyses with behavioral data.

Results

Study Participants

Demographic and behavioral data are described in Table 1. BOLD response was unrelated to lifetime psychiatric history.

Imaging Analysis

Main Effect Neural Activation During Sucrose Taste Processing—To confirm task-related activation of the main neural substrates that are known to process sweet taste (18), we examined activation in response to sucrose stimulation using a stimulus versus baseline voxel-based statistical masked by *a priori* regions of interest that are engaged by taste circuitry. For all three groups, there was main effect activation during sucrose administration (Figure 1, Table 2) in the ventroposterior nuclei of the thalamus, anterior insula, and pregenual anterior cingulate (BA 24/32). Main effect activations were relatively similar for sucralose (Table 2). A whole brain analysis was performed to investigate which

regions outside the predetermined regions of interest also showed activation (data not shown). While the areas largely confirmed the region of interest analysis, additional areas of consistent activation were observed extending into the thalamus and in the prefrontal gyrus in the control women group and bilateral insula activation during sucralose in women recovered from bulimia nervosa (Table S2).

Group-by-condition analysis—A significant group (controls/women recovered from anorexia/women recovered from bulimia) by condition (sucrose/sucralose) interaction was identified, centered in the dorsal aspect of the right insula, ($F(2,51)=10.72$, $p<0.001$) and right dorsal caudate ($F(2,51)=8.91$, $p=0.001$) for a voxel-based ANOVA ($p<0.05$) masked by *a priori* regions of interest (Figure 2). Whole-brain analysis provided similar regions (Table S2).

Right Insula and Dorsal Caudate Post-hoc: Within-condition analysis—Tastes of sucrose corresponded with significantly decreased right anterior insula activation in women recovered from anorexia ($F(1,27)=7.79$, $p=0.010$) and increased activation in women recovered from bulimia ($F(1,27)=6.12$, $p=0.020$) compared to control women (Figure 2B, Table 3). A similar activation pattern in response to the sucrose stimulus was found in the right dorsal caudate. Though activation did not reach significance, it indicated a decreased response in women recovered from anorexia relative to the control women group ($F(1,27)=3.35$, $p=0.079$) (Figure 2C, Table 3). Tastes of sucralose also corresponded with a significant decrease in right anterior insula activation ($F=4.980$, $p=0.035$) in women recovered from anorexia compared to control women (Figure 2B, Table 3), while right anterior insula activation for women recovered from bulimia nervosa was similar to control women. The trend of a decreased right dorsal caudate response in women recovered from anorexia versus control women ($F=3.602$, $p=0.069$) was also seen in the sucralose condition, while women recovered from bulimia showed a decreased, but non- significant, activation in comparison to control women (Figure 2C, Table 3).

Comparison of sucrose to sucralose: Within-group analysis—When sucrose was compared to sucralose, women recovered from anorexia ($F(1,13)=10.131$, $p=0.007$) and bulimia ($F(1,13)=8.210$, $p=0.013$) demonstrated significant differences in right anterior insula, but in opposite directions (anorexia nervosa: sucrose<sucralose; bulimia nervosa: sucrose>sucralose) (Table 3). The same difference and directionality were observed in the right dorsal caudate when comparing sucrose and sucralose in both women recovered from anorexia ($F(1,13)=7.909$, $p=0.015$) and bulimia ($F(1,13)=5.975$, $p=0.030$).

Behavioral Relationships—There were no significant brain-behavior relationships after correcting for multiple comparisons (Table S3).

Discussion

This is the first fMRI study to compare sweet taste response between women recovered from anorexia and bulimia nervosa and controls. Within corticolimbic circuits involved in appetite regulation (Figure 1), we found that right anterior insula response to sucrose was diminished in women recovered from anorexia and exaggerated in women recovered from bulimia nervosa when compared to controls.

Other studies investigating response to tastes of foods have shown abnormal insula response in anorexia nervosa. We replicated a previous study from our group that found that women recovered from anorexia had diminished hemodynamic response in the anterior insula to tastes of sucrose or water (10). Vocks (19) compared hunger and satiety states while

drinking chocolate milk and showed that, in the hungry state, subjects who were ill with anorexia nervosa activated the insula less than controls.

The anterior insula is well established as the primary taste cortex (see Appendix), which integrates the sensation of taste with multiple bodily sensations to generate an 'internal milieu,' or the 'interoceptive state' (7, 20). The anterior insula, as part of limbic sensory cortex (21), is involved in representations of the hedonic state of the individual. Thus, altered neural signaling in the anterior insula could suggest a dysregulation of hedonic-taste processing in eating disorder individuals. Prior investigations have shown normal perception of sweet taste in subjects with eating disorders (22). Instead, consistent with prior studies (22) (see Appendix), our results of altered sweet taste preference support the hypothesis of altered neural representation of hedonic valuation in eating disorders.

The connectivity of the anterior insula with other brain areas that are important for reward related processing implies that the emotional value of interoceptive cues such as taste or feelings of hunger or fullness are computed in the anterior insula (21). This brain area has been implicated in a contextualized representation of the 'feeling' self in time and with respect to maintenance of a homeostatic state. For example, a current state, such as food deprivation, is compared with a previous state of homeostasis, and this information is then integrated in the formation of emotions (23, 24). Sweet tastes, such as those delivered in our study, are processed against this 'interoceptive-hedonic' backdrop.

Brain imaging studies giving tastes of sugar to healthy individuals in food deprived versus satiated states have consistently shown that receipt of sucrose in the food deprivation state results in relatively higher activation in the insula and orbitofrontal cortex, potentially reflecting perceived change in interoceptive state (25) (see Appendix). In this study, we fed subjects a modest meal prior to the fMRI scan and thus did not test extremes of feeding or food deprivation. Still, these data raise clinically relevant questions with regard to how symptoms in eating disorders may be related to erroneous interoceptive feedback. The relatively lower activation of insula signal in individuals recovered from anorexia nervosa suggests a signal consistent with relatively high satiation. Attenuated anterior insula activation in anorexia nervosa could therefore reflect a hunger signal that is attenuated compared to the fed state. In a clinically ill population, the attenuated signal associated with sweet taste may not provide a sufficient learning signal to change behavior (e.g. eating more in the state of food deprivation), resulting in a rigid behavioral phenotype.

From another perspective, individuals with anorexia nervosa may simply fail to accurately recognize hunger due to altered homeostatic interoceptive signals. There might be a discrepancy between their perceived internal body state (full, bloated) and their actual internal body state (calorie-deficient) causing them to avoid food when internal cues should in fact be driving them to eat. In contrast, based on data from healthy controls (25), the relatively higher insula activation in our women recovered from bulimia nervosa may be consistent with the opposite: exaggerated hedonic response to sweet taste together with an interoceptive status of relative hunger. Increased anterior insula activation in bulimia nervosa could represent an exaggerated interoceptive perception of hunger/deprivation signal, which may mutually amplify the reward and homeostatic systems, leading to excessive episodic food intake. While not investigated in this study, it is also possible that other eating disorder symptoms, such as body image distortion, alexythmia, and lack of insight and motivation to change, could be part of a more generalized disturbance related to interoceptive processing (10).

Dorsal caudate response

Our study demonstrated a trend toward reduced dorsal caudate response to tastes of sucrose and sucralose in women recovered from anorexia nervosa. This parallels the insula findings and is in accordance with prior work showing that women recovered from anorexia had diminished bilateral dorsal caudate, dorsal putamen, and ventral putamen hemodynamic response to tastes of sucrose and water (10). Another study in women recovered from bulimia nervosa (26) showed an exaggerated anterior ventral striatum response for a cream/water contrast compared to women recovered from anorexia nervosa and controls. The striatum receives direct inputs from the insula (27, 28) and this path is thought to mediate eating behavior, which may have a direct impact on the types of palatable foods avoided or over-consumed in eating disorders (29). These striatal findings, in conjunction with insula alterations, raise the possibility that there may be a disturbance in the mechanisms translating interoceptive signals into enhanced or diminished motivated eating.

Sweetness versus energy content of sucrose

Women recovered from anorexia and bulimia nervosa also showed differences in response to sucrose versus sucralose in the right anterior insula and right dorsal caudate. No group showed hypothalamic differences. In the right anterior insula, women recovered from anorexia nervosa showed greater response to sucrose than sucralose while women recovered from bulimia nervosa showed greater response to sucralose than sucrose (**data not shown**). This suggests that sucralose as a contrast solution successfully distinguished between processing of caloric versus non-caloric sweet tastes. In contrast, for control women, sucrose was similar to sucralose in the anterior insula, and sucralose showed greater activation in the caudate. A previous analysis of data from controls (30) supports the speculation (31) that sucrose, through effects on insula signaling, may result in changes of dopamine transmission that could modify the relative association of energy value of sucrose to its motivational value. These findings raise the possibility that individuals with anorexia and bulimia nervosa have altered balance or sensitivity regarding mechanisms that signal the caloric content of foods versus gustatory pathways that code the sweetness of foods.

Limitations

The study of eating disorders frequently raises questions regarding cause and consequence: Do neurobiological disturbances cause pathological eating behaviors, or are neurobiological disturbances secondary to abnormal nutrition? Our literature review reveals some consistency of results in ill and recovered eating disorder subjects, suggesting these findings could be traits, but there is sparse evidence from direct comparisons using the same design, and no longitudinal studies. Even if persistent psychophysiological disturbances in recovered eating disorders are “scars,” they are still likely to help understand the processes contributing to these disorders. These ideas could be tested in children at-risk for eating disorders, to see if these neural signatures are predictive of illness development. It should be noted that there are discrepant insula findings in other gustatory studies (32–35) that might be related to anticipatory responses (36) (see Appendix). As our study task did not include an explicit expectation phase, this may contribute to some discrepant results across studies. Other functional MRI studies of appetite in eating disorders have employed designs that used pictures of food or food words (37, 38). Pictures may elicit different brain responses, so this literature is not examined here. Artificial sweeteners are not identical to sugars in terms of how they activate tongue sweet receptors (39) (see Appendix). It is possible that a mismatch in sweetness, rather than added caloric content, contributed to the observed differences between sucrose and sucralose. The use of atlas-based regions-of-interest analysis may limit the capacity to detect signal in regions where recovered individuals show differences in brain structure (40). Although the Gaussian filter that was applied helps

correct for some level of individual differences in brain structure, an attenuated or absent effect may represent a false negative due to group deviations from the standardized atlas. While the sample size of each cohort was relatively modest, the findings were robust. Compared to other behavioral disorders, eating disorder individuals have homogenous symptoms, so that smaller samples may be adequate to show group differences.

Treatment Implications

Aberrant function of the right anterior insula, which integrates gustatory stimuli and interoceptive/hedonic signals, may contribute to a failure of higher order appetitive processes to reach homeostasis and thus lead to pathological eating behaviors. Attenuated anterior insula response in anorexia nervosa and exaggerated insula activity in bulimia nervosa raise the possibility that these disorders comprise, respectively, an overly rigid or highly unstable neural representation of internal feeling states at the junction of feeding and, possibly, emotive decision-making. Identifying abnormal neural substrates in these individuals helps to reformulate the basic pathology of eating disorders and offers targets for novel approaches to treatments. It may be possible to modulate the experience by enhancing insula reactivity when individuals with anorexia nervosa engage in eating behavior, or dampening exaggerated or possibly unstable responses to food in individuals with bulimia nervosa. One approach is the use of techniques that might “train” the insular cortex. Studies have shown that healthy subjects can use real-time fMRI to control right anterior insula activity.(41) Biofeedback might be also be useful since there is evidence that it helps individuals with anxiety disorders to observe inaccuracies in perceiving physiological activity, or to strengthen perception when actual somatic changes occur.(42) A second approach, it may be possible to modify existing therapies so they can better target eating disorder psychopathology. For example, to behaviorally modulate the insula by increasing the influence of top-down modulation, i.e. inhibiting the urge to eat in bulimic individuals by employing cognitive training. Alternatively, studies suggest that mindfulness training alters cortical representations of interoceptive attention.(43, 44) Or, a dialectical behavioral therapy approach may be used to promote development of more effective strategies for recognizing, predicting, and constructively managing tendencies to have rigid or unstable responses to stimuli. From another perspective, if those with anorexia nervosa have an overly active satiety signal in response to palatable foods, it may be worthwhile to try strategies, such as avoiding highly palatable foods, in favor of bland, dilute, or even slightly aversive foods, and perhaps recommend multiple small meals of equivalent daily calories, in order to avoid overstimulation and early satiety. Finally, pharmacological modulation of insular reactivity might increase sensitivity to food in anorectic individuals or attenuate hyper-responsivity in bulimic patients. For example, recent studies in healthy controls(45) show that olanzapine enhances reward response toward food in brain reward circuitry and decreases inhibition to food consumption in regions thought to inhibit feeding behavior. In summary, an understanding of the basic pathophysiology of anorexia and bulimia nervosa provides rationales and heuristics to develop improved treatments for these chronic and deadly disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. APA. Association AP. Diagnostic & Statistical Manual of Mental Disordes: DSM:VI-TR. 4. Washington, DC: 2000.
2. Kaye W, Fudge J, Paulus M. New insight into symptoms and neurocircuit function of anorexia nervosa. Nat Rev Neurosci. 2009; 10(8):573–84. [PubMed: 19603056]
3. Kaye W. Neurobiology of anorexia and bulimia nervosa. Physiology and Behavior. 2008; 94:121–35. [PubMed: 18164737]
4. Berthoud H. Homeostatic and non-homeostatic pathways involved in the control of food intake and energy balance. Obesity. 2006; 14(Suppl 5):197S–200S. [PubMed: 17021366]
5. Volkow N, Wang G, Baler R. Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci. 2011; 15(1):37–46. [PubMed: 21109477]
6. Rolls E. Sensory processing in the brain related to the control of food intake. Proc Nutr Soc. 2007; 66(1):96–112. [PubMed: 17343776]
7. Small D. Central gustatory processing in humans. Adv Otorhinolaryngol. 2006; 63:191–220. [PubMed: 16733340]
8. Couturier J, Lock J. What is recovery in adolescent anorexia nervosa? Int J Eat Disord. 2006; 39(7): 550–5. [PubMed: 16791851]
9. Wagner A, Barbarich N, Frank G, Bailer U, Weissfeld L, Henry S, Achenbach S, Vogel V, Plotnicov K, McConaha C, Kaye W, Wonderlich S. Personality traits after recovery from eating disorders: Do subtypes differ? International Journal of Eating Disorders. 2006; 39(4):276–84. [PubMed: 16528697]
10. Wagner A, Aizenstein H, Frank GK, Figurski J, May JC, Putnam K, Bailer UF, Fischer L, Henry SE, McConaha C, Kaye WH. Altered insula response to a taste stimulus in individuals recovered from restricting-type anorexia nervosa. Neuropsychopharmacology. 2008; 33(3):513–23. [PubMed: 17487228]
11. Silver I, Erecinska M. Glucose-induced intracellular ion changes in sugar-sensitive hypothalamic neurons. J Neurophysiol. 1998; 79(4):1733–45. [PubMed: 9535943]
12. Chandraskekar J, Hoon M, Ryba N, Zuker C. The receptors and cells for mammalian taste. Nature. 2006; 444:288–94. [PubMed: 17108952]
13. Knight I. The development and applications of sucralose, a new high-intensity sweetener. Can J Physiol Pharmacol. 1994; 72:435–9. [PubMed: 7922876]
14. First, MB.; Gibbon, M.; Spitzer, RL.; Williams, JBW. Users guide for the structured clinical interview for DSM-IV Axis I disorders- research version (SCID-I, version 2.0, February 1996). New York: Biometrics Research Department, New York State Psychiatric Institute; 1996.
15. Beck AT, Ward M, Mendelson M, Mock J, Erbaugh J. An Inventory for measuring depression. Arch Gen Psychiatry. 1961; 4:561–71. [PubMed: 13688369]
16. Cloninger, CR.; Przybeck, TR.; Svrakic, DM.; Wetzel, RD. The Temperament and Character Inventory (TCI): A Guide to its Development and Use. St. Louis, MO: Center for Psychobiology of Personality, Washington University; 1994. p. 19-28.
17. Spielberger, CD. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, Inc; 1983.
18. Small D. Individual differences in the neurophysiology of reward and the obesity epidemic. Int J Obes. 2009; 33(Suppl 2):S44–8.
19. Vocks S, Herpertz S, Rosenberger C, Senf W, Gizewski E. Effects of gustatory stimulation on brain activity during hunger and satiety in females with restricting-type anorexia nervosa: An fMRI study. J Psychiatr Res. 2011; 45:395–403. [PubMed: 20709330]
20. Kurth FZK, Fox P, ARL, Eickhoff S. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Structure and Function. 2010; 214(5–6):519–34. [PubMed: 20512376]
21. Craig A. How do you feel--now? The anterior insula and human awareness. Nature Rev Neuroscience. 2009; 10(1):59–70.
22. Sunday SR, Halmi KA. Taste perceptions and hedonics in eating disorders. Physiol Behav. 1990; 48(5):587–94. [PubMed: 2082356]

23. Paulus M, Stein MB. An insular view of anxiety. Biol Psychiatry. 2006; 60(4):383–7. [PubMed: 16780813]
24. Craig A. The sentient self. Brain Struct Funct. 2010; 214(5–6):563–77. [PubMed: 20512381]
25. Haase L, Cerf-Ducastel B, Murphy C. Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. Neuroimage. 2009; 44(3):1008–21. [PubMed: 19007893]
26. Radeloff D, Willmann K, Otto L, Lindner M, Putnam K, van Leeuwen S, Kaye W, Poustka F, Wagner A. High-fat taste challenge reveals altered striatal response in women recovered from bulimia nervosa - a pilot study. [Epub ahead of print]. World J Biol Psychiatry. 2012
27. Chikama M, McFarland N, Amaral D, Haber S. Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. J Neurosci. 1997; 17(24):9686–705. [PubMed: 9391023]
28. Fudge J, Breitbart M, Danish M, Pannoni V. Insular and gustatory inputs to the caudal ventral striatum in primates. J Comp Neurol. 2005; 490(2):101–18. [PubMed: 16052493]
29. Berridge K, Ho C, Richard J, Deifeliceantonio A. The tempted brain eats: Pleasure and desire circuits in obesity and eating disorders. Brain Res. 2010; 1350:43–64. [PubMed: 20388498]
30. Frank G, Oberndorfer T, Simmons A, Paulus M, Fudge J, Yang T, Kaye WH. Sucrose activates human taste pathways differently from artificial sweetener. NeuroImage. 2008; 39:1559–69. [PubMed: 18096409]
31. Zink C, Weinberger D. The rewards of self starvation. Nature Med. 2010; 16(12):1382–3. [PubMed: 21135849]
32. Cowdrey F, Park R, Harmer C, McCabe C. Increased neural processing of rewarding and aversive food stimuli in recovered anorexia nervosa. Biol Psych. 2011; 70(8):736–43.
33. Frank G, Reynolds J, Shott M, Jappe L, Yang T, Tregellas J, O'Reilly R. Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharm. 2012; 37(9): 2031–46.
34. Bohon C, Stice E. Reward abnormalities among women with full and subthreshold bulimia nervosa: a functional magnetic resonance imaging study. Int J Eat Disord. 2011; 44(7):585–95. [PubMed: 21997421]
35. Frank G, Reynolds J, Shott M, O'Reilly R. Altered temporal difference learning in bulimia nervosa. Biol Psych. 2011; 70(8):728–35.
36. Stice E, Spoor S, Bohon C, Small D. Relation between obesity and blunted striatal response to foods is moderated by TaqIA A1 allele. Science. 2008; 322(5900):449–52. [PubMed: 18927395]
37. Brooks S, O'Daly O, Uher R, Frederich H-C, Giampietro V, Brammer M, Williams S, Schioth H, Treasure J, Campbell I. Differential neural responses to food images in women with bulimia versus anorexia nervosa. Public Library of Science One. 2011; 6(7):1–8.
38. Giel K, Friederich H, Teufel M, Hautzinger M, Enck P, Zipfel S. Attentional processing of food pictures in individuals with anorexia nervosa--an eye-tracking study. Biol Psych. 2011; 69(7):661–7.
39. Nie Y, Vigues S, Hobbs J, Conn G, Munger S. Distinct contributions of T1R2 and T1R3 taste receptor subunits to the detection of sweet stimuli. Curr Biol. 2005; 15:1948–52. [PubMed: 16271873]
40. Lambe EK, Katzman DK, Mikulis DJ, Kennedy SH, Zipursky RB. Cerebral gray matter volume deficits after weight recovery from anorexia nervosa. Arch Gen Psychiatry. 1997; 54(6):537–42. [PubMed: 9193194]
41. Caris A. Regulation of anterior insula cortical activity using real-time fMRI. Neuroimage. 2007; 35:1238–46. [PubMed: 17336094]
42. Domschke K, Stevens S, Pfleiderer B, Gerlach A. Interoceptive sensitivity in anxiety and anxiety disorders: An overview and integration of neurobiological findings. Clin Psychol Rev. 2010; 30:1–11. [PubMed: 19751958]
43. Farb N, Segal Z, Anderson A. Mindfulness meditation training alters cortical representations of interoceptive attention. 2012

44. Lutz A, McFarlin DPDM, Salomons T, Davidson R. Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. Neuroimage. 2012; 64C:538–546. [PubMed: 23000783]

45. Mathews J, Newcomer J, Mathews J, Fales C, Pierce K, Aikers B, Marcu I, Barch D. Neural correlates of weight gain with olanzapine. Arch Gen Psychiatry. 2012; 69(12):1226–37. [PubMed: 22868896]

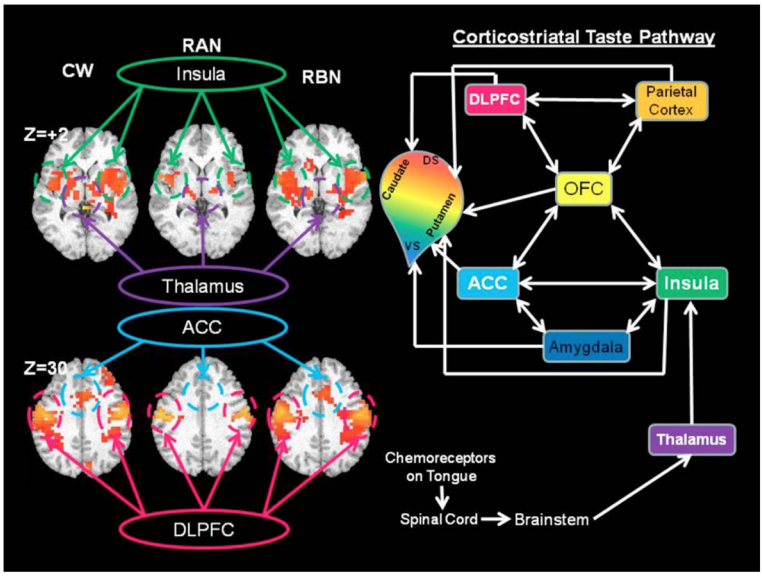

Figure 1.

Main effect neural activation during sucrose taste processing. Taste pathway: Chemoreceptors on the tongue detect the sweet taste. This signal transmits through the spinal cord and into the brainstem. The thalamus (purple) relays this information to the primary gustatory cortex, which is interconnected with the anterior insula (green). The anterior insula is a vital component of the ventral neurocircuit, or limbic system, through its connections with the amygdala (blue), the anterior cingulate cortex (ACC; turquoise) and the orbitofrontal cortex (OFC; yellow). Afferents from cortical structures involved in the ventral neurocircuit are directed to the ventral striatum (VS); cortical structures more involved in cognitive strategies, forming a dorsal neurocircuit that includes the dorsolateral prefrontal cortex (DLPFC; pink), send inputs to the dorsal striatum (DS).

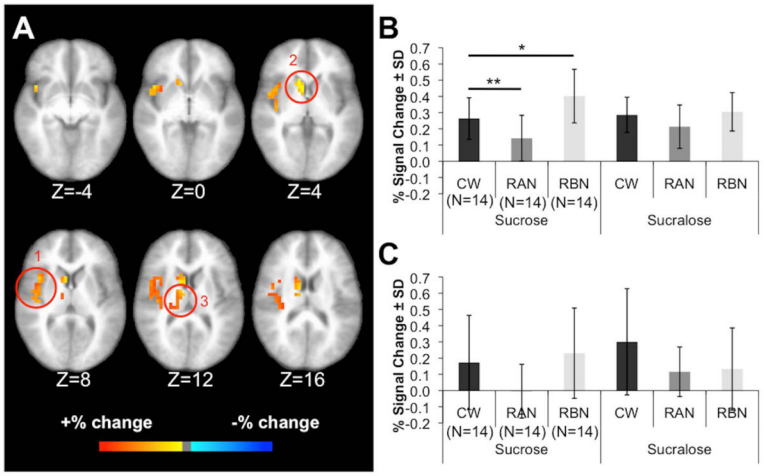

Figure 2.

Group by condition interactions. (A) Regions of interest were defined by a one-way group (CW, RAN, RBN) by condition (Sucrose, Sucralose) ($p<0.05$) analysis of variance. Center of mass in Talairach XYZ coordinates. Region 1: Anterior insula (5504 mm^3, 86 voxels, XYZ=39,-2,8). Region 2: Dorsal caudate (1984 mm^3, 31 voxels, XYZ=10,9,8). Region 3: Thalamus (1088 mm^3, 17 voxels, XYZ=12,-12,12). (B) Post-hoc t-tests in the right anterior and middle insula showed that response to sucrose was significantly less in women recovered from anorexia nervosa (RAN) versus control women (CW) (** $p<0.01$) but significantly greater in women recovered from bulimia nervosa (RBN) versus CW (* $p<0.05$). (C) Post-hoc t-tests in the right dorsal caudate showed decreased response to sucrose in RAN versus CW that approached significance ($p=0.079$). No significant condition or group activation differences were observed in the right thalamus (Region 3, data not shown).

Table 1

Demographic and behavioral data. Subject comparisons for lifetime high and low BMI, behavioral measures, the dose of sucralose that matched a 10% sucrose solution, and Subjects subjective “pleasantness” rating of a 10% sucrose solution.

	CW		RAN		RBN		
	Avg	**SD**	**Avg**	**SD**	**Avg**	**SD**	**P**
Age (years)	27.4	5.5	27.3	1.4	26.6	5.7	N.S.
Recovered (years)	-	-	5	1.6	2.7	1.3	N.S.
Illness Duration (years)	-	-	8.2	1.7	8	5.9	N.S.
BMI	22.6	1.5	21.5	2.8	22.9	2.1	N.S.
Low lifetime BMI	20.4	1.3	14.9	2.6	19.7	1.9	<0.001
High lifetime BMI	23	1.6	23.6	3	25.7	2.6	0.02
Harm Avoidance (TCI)	10	5	13	2	16	7	0.03
Depression (BDI)	3	3	6	1	5	4	N.S.
State Anxiety (STAIY)	26	9	30	2	30	13	N.S.
Trait Anxiety (STAIY)	28	9	30	3	31	13	N.S.
Splenda (g) †	1.3	0.1	1.5	0.1	1.5	0.3	0.02
Sucrose Pleasantness	4.1	2.1	4.9	0.5	4.1	2	N.S.

† While RAN (F(1,27)=7.664, p=0.010) and RBN (F(1,27)= 8.935, p=0.006) required more sucralose to taste match with sugar than controls, when asked after the fMRI scan all subjects reported that they were unable to distinguish between sucrose and sucralose solutions. Average (Avg). Standard Deviation (SD). Probability (Prob). Body mass index (BMI). Control Women (CW). Women recovered from anorexia nervosa (RAN). Women recovered from bulimia nervosa (RBN). Temperament and Character Inventory (TCI), Beck Depression Inventory (BDI), State Trait Anxiety Inventory Y (STAI-Y).

Table 2

Main effect BOLD signal response to sucrose and sucralose in regions of interest. Thresholded at $p<0.005$ significance and a minimum cluster size of 8 contiguous voxels (512 mm^3).

		CW					RAN					RBN				
Condition	**Regions**	**mm^3**	**#**	**X**	**Y**	**Z**	**mm^3**	**#**	**X**	**Y**	**Z**	**mm^3**	**#**	**X**	**Y**	**Z**
Sucrose	**Insula**	5952	93	40	−7	9	3456	54	40	−9	11	10368	162	42	−7	9
		5824	91	−40	−4	9	4032	63	−39	−9	11	10176	159	−40	−8	10
	Thalamus	2688	42	14	−19	10	2816	44	12	−17	8	4672	64	11	−15	10
		832	13	−11	−13	7	1600	25	−11	−16	7	4352	68	−11	−16	9
	Middle Frontal Gyrus	640	10	37	35	27	n/a	n/a				896	14	35	41	25
		960	15	−32	36	26	n/a	n/a				1664	26	−35	33	24
	Supragenual ACC	6144	96	−2	4	39	1728	27	1	5	38	16256	254	4	0	35
	Caudate	n/a	n/a				n/a	n/a				1216	19	−11	15	4
Sucralose	**Insula**	8960	140	42	−8	10	4608	72	40	−7	11	9664	151	42	−8	10
		6848	107	−40	−6	8	5824	91	−40	−8	10	9472	148	−40	−9	11
	Thalamus	5760	90	12	−17	10	2944	46	12	−17	9	4224	66	12	−15	10
		3904	61	−11	−16	9	1536	24	−12	−16	7	4480	70	−11	−17	9
	Middle Frontal Gyrus	1344	21	35	37	26	n/a	n/a				8320	130	3	8	37
		832	13	−34	42	23	n/a	n/a				n/a	n/a			
	Supragenual ACC	11840	185	2	4	38	3520	55	2	6	37	n/a	n/a			
	Midbrain	512	8	8	−19	−11	n/a	n/a				512	8	8	−19	−10

The volume of each voxel is 64 mm^3. XYZ coordinates center of mass in Talairach space. Control Women (CW). Women recovered from anorexia nervosa (RAN). Women recovered from bulimia nervosa (RBN). Volume (Vol). Anterior cingulate cortex (ACC).

Table 3

Summary of ANOVA comparisons from the right (R) anterior insula and R dorsal caudate in control women (CW), women recovered from anorexia nervosa (RAN), and women recovered from bulimia nervosa (RBN).

	R Anterior Insula		R Dorsal Caudate	
	F	**P**	**F**	**P**
Groups	**Group x Condition Differences**			
CW, RAN, RBN	10.722	<0.001	8.907	0.001
CW, RAN	2.539	0.123	0.015	0.905
CW, RBN	8.917	0.006	13.755	0.001
	Sucrose-Sucralose Group Differences			
CW, RAN, RBN	7.036	0.002	2.088	0.138
CW, RAN	4.460	0.044	4.264	0.049
CW. RBN	2.964	0.097	0.280	0.601
	Sucrose-Only Group Differences			
CW, RAN, RBN	12.752	<0.001	2.864	0.069
CW, RAN	7.787	0.010	3.346	0.079
CW, RBN	6.120	0.020	0.280	0.601
	Sucralose-Only Group Differences			
CW, RAN, RBN	3.848	0.030	2.238	0.121
CW, RAN	4.980	0.035[1]	3.602	0.069[6]
CW, RBN	0.191	0.666[2]	2.303	0.141[7]
	Condition Differences			
CW	1.105	0.312[3]	7.780	0.015[8]
RAN	10.131	0.007[4]	7.909	0.015[9]
RBN	8.210	0.013[5]	5.975	0.030[10]

In the right anterior insula (AI) region defined by the group-by-condition contrast, response to sucralose was significantly lower in RAN compared to CW[1] but was not significantly different between CW and RBN[2]. Sucrose elicited greater BOLD signal than sucralose for RBN subjects[5] in the right AI, while the BOLD response was lower in sucrose versus sucralose for RAN subjects[4]. CW showed no condition differences[3] in the right AI. In the right caudate region defined by the group-by-condition contrast, decreased sucralose response compared to control women did not reach significance in either recovered anorexic[7] or recovered bulimic[7] groups. Sucrose elicited greater BOLD signal than sucralose for recovered bulimic subjects[10] in the right caudate, while the BOLD response was lower in sucrose versus sucralose for both recovered anorexics[9] and control women[8].