Data Supplement for Oberndorfer et al., Altered Insula Response to Sweet Taste Processing After Recovery From Anorexia and Bulimia Nervosa. Am J Psychiatry (doi: 10.1176/appi.ajp.2013.11111745)

Supplementary Methods and Tables

We used standard methods for this study, but we provide more details here in order to facilitate replication.

Subject lifetime comorbid diagnoses:
Lifetime comorbid diagnosis in women recovered from anorexia nervosa included: Major Depressive Disorder (n=8), Obsessive-Compulsive Disorder (n=8), Post-Traumatic Stress Disorder (n=5), Specific Phobia (n=4), Social Phobia (n=4), Trichotillomania (n=3), Alcohol Dependence (n=2), Body Dysmorphic Disorder (n=2), Panic Disorder (n=2), Cannabinoid Dependence (n=1), and Generalized Anxiety Disorder (n=1). Comorbidities in women recovered from bulimia nervosa included: Major Depressive Disorder (n=11), Obsessive-Compulsive Disorder (n=11), Social Phobia (n=5), Specific Phobia (n=4), Alcohol Dependence (n=4), Cannabinoid Dependence (n=4), Cocaine Dependence (n=3), Trichotillomania (n=2), Body Dysmorphic Disorder (n=2), and Post-Traumatic Stress Disorder (n=1). Comorbidities in the CW group included: Major Depressive Disorder (n=1), Specific Phobia (n=1), and Alcohol Dependence (n=1).

Additional Methodological Details are provided so that others can replicate the findings in this study.

Matching of non-caloric sweetener:
We wanted to control for the possibility that AN, BN, and control women have a difference in sensitivity to sweet taste, or aversive or hedonic response (aversive versus hedonic) to a sweet taste. Some but not all studies suggest women with anorexia and bulimia nervosa have altered sweet taste perception compared to healthy control women (1-4).

Thus, we developed a paradigm (5) in which subjects individually matched the sweetness of an artificial sweetener solution (sucralose, commercial Splenda®, McNeil Nutritionals, Ft. Washington PA) to a sucrose solution.. Prior to the imaging study, and during the follicular phase of the menstrual cycle, each subject was tested to find an adjusted “dose” of sucralose that matches the subjective sweetness experienced by each subject tasting the 10% sucrose solution. Subjects could not distinguish between pleasantness of the 10% sucrose (Table 1). The individualized concentration of sucralose was subsequently used for the brain imaging study, during which the 10% sucrose (Mallinckrodt Chemicals, Phillipsburg NJ) and dose-matched sucralose were administered in a fixed random order (pseudorandom) in two blocks consisting of 20 total stimuli, each separated by 20 seconds. A second taste test determined individual hedonic response to sucrose solutions with a range of concentrations (5) using sucrose solutions (concentrations 0, 2, 4, 8, 10, 16, and 32%) and a corresponding set of Sucralose solutions matched for sweetness according to manufacturer conversions (5). Hedonic and sensory perception of sucrose and sucralose were assessed on 9-point Pleasantness (from 1, “like not at all,” to 9, “like extremely”) and Sweetness (from 1, “absent,” to 9, “extremely sweet”) scales. Sucrose and sucralose solutions were given blindly and in random order. Moskowitz *et al*. reported that, in healthy control subjects, sweetness ratings show positive linear slopes with increasing concentration across simple and complex carbohydrates (6). Pleasantness response, in contrast, varies across type of sugar and subject population (7). Behavioral data were analyzed with SPSS 14 (SPSS, Chicago, Illinois) and statistiXL 1.8 (http://www.statistixl.com/) statistical software. Both women recovered from anorexia and women recovered from bulimia nervosa needed a higher dose of sucralose compared to control women in order to not consciously distinguish the two taste stimuli, which creates a possible between-group confound.

Taste solution delivery:
Sucrose and sucralose solutions were delivered with a programmable syringe pump (J-Kem Scientific, St. Louis MO) in 1-mL per second stimulations (8). Two sterile silicone tubes were placed securely in the center of the tongue immediately adjacent to each other. Subjects were told that they would receive 1-mL tastes of either sugar or sucralose solutions every 20 seconds, that there would be 20 such tastes in a block, and that they would complete six blocks. They were instructed to keep their eyes closed during the scan, to swish once and swallow after each taste stimulus, and to avoid sucking on the tubes. Two blocks

of sweet taste stimulation were applied: one was a 10% concentration of sucrose (Mallinckrodt, USA) and the second was a sucralose solution individually matched to sweet taste perception of the sucrose solution. Sweet tastes were delivered in pseudo-randomized order. Each block consisted of 20 one-mL taste stimulations 20 seconds apart, half of which were sucrose and half sucralose. The data presented in this study are derived solely from these pseudo-randomized blocks. Four additional taste blocks were administered: two blocks of 20 repeated sucrose stimulations, and two blocks of 20 repeated sucralose stimulations. Subjects ingested a total of 6 grams sucrose (24 Kcal) over 30 minutes. We used a 10% sucrose solution, which is a level of sweetness preferred by the general public and present in soft drinks (9), and on the day before the fMRI study, each subject was tested in order to identify a sucralose solution that was matched to the sweetness of the 10% sucrose solution for that individual. Subjects were trained to place the tubes in the center of their tongue, not too far forward and not too far back, to swish once and swallow after each taste stimulus, and to avoid sucking on the tubes. All subjects reported that they felt comfortable with these instructions and did not need to practice this swish and swallow action prior to scan.

Additional Discussion is intended to provide a more complete context for the current study.

Sweet taste perception and hedonics:

Women with anorexia or bulimia nervosa show no difference of taste perception (either sweetness or fat content) compared to healthy controls, either while ill or after treatment (1, 3, 10). However, individuals with anorexia and bulimia nervosa preferred sweeter solutions with lower fat content (1, 3, 10). Hedonic preference to sweet taste alone varied across studies, with one study (1) finding no difference in women with anorexia or bulimia nervosa compared to controls and others finding decreased sweet taste preference in women recovered from anorexia nervosa (3, 10-12). Interestingly, the difference of hedonic response is most robust in solutions with the lowest sucrose concentrations, despite no disturbance of sweet taste perception (10, 11). Together, this literature suggests that differences of sweet taste perception likely do not underlie altered insula response to sucrose in women recovered from anorexia and bulimia nervosa, though differences of hedonic response may be relevant.

Insula subdivisions:

The insula was selected as an important region for the integration of affective and physiological information. It is arranged longitudinally from the most somatic aspects in the posterior and the most integrative in the anterior (13). Functional divisions of the insula are based on cytoarchitectural, connectional and behavioral studies in higher primates (14-16). In general, the anterior, less differentiated half of the insula receives the majority of projections from the amygdala and thalamic taste centers, making it an ideal site for the formulation of hedonic representations of taste. We included the full extent in the mask in order to assess the integrated and incremental architecture.

Insula response during anticipation of gustatory stimuli:

It should be noted that there are discrepant insula findings in other gustatory studies that might be related to anticipatory responses. Recent studies in obesity (17) have highlighted the importance of anticipation in the neural response to food stimuli. Women recovered from anorexia nervosa (18) had increased ventral striatal activity in response to sights and flavors of pleasant stimuli (chocolate) and increased insula and posterior dorsal caudate response to flavors and sights of aversive foods when compared to controls. Frank (19) performed an associative learning task between conditioned visual stimuli and unconditioned sucrose taste stimuli and found that unexpected reward learning signals were greater in subjects who were ill with anorexia nervosa and less in obese participants compared to the controls in the anterior ventral striatum, insula, and orbital frontal cortex. Furthermore, in bulimia nervosa, Bohon & Stice (20) found that, compared to controls, women ill with bulimia nervosa showed trends toward hypoactivation in the right anterior insula in response to anticipated receipt of chocolate milkshake, and in the left middle frontal gyrus and insula regions in response to consumption of milkshake (versus tasteless solution). In another study (21), women who were ill with bulimia nervosa showed reduced brain response compared with controls for unexpected receipt and omission of taste stimuli in insula, ventral putamen,

amygdala, and orbital frontal cortex. As our study task did not include an explicit expectation phase, we highlight the perceptual differences with the understanding that additional differences in learning and anticipation contribute to neurocognitive mechanisms of eating disorders, and this may contribute to some discrepant results across studies.

Lack of findings in the orbitofrontal cortex (OFC)

It is important to emphasize that other neural substrates beside the insula contribute to the complex signal of food in general and sweet taste in particular. Some studies argue that the anterior insula is important for a hunger- and reward-independent representation of food in the mouth (22), whereas the OFC, anterior and inferior to the insula, computes the state-dependent hedonic value of food (22-24). Alternatively, there is evidence (25-27) that both the anterior insula and OFC integrate the sensory representations of taste with its incentive value. This study did not identify main effect OFC response to sucrose or sucralose despite this region's involvement in taste processing. Also, no group or condition differences were identified in the OFC.

The OFC has been associated with flexible responses to changing stimuli (28), including changes in the incentive value of a stimulus. For example, the incentive value of food depends on whether an animal is hungry (29-31). We did not observe findings in the OFC. The lack of OFC findings could be due to frontal sinus artifacts, which decreases the signal-to-noise ratio and therefore lower the power to detect differences in these regions. However, another group (32) that used the same equipment at UCSD, found inferior prefrontal activation in response to sucrose when contrasting hunger and satiety. Neurons in the secondary gustatory cortex may be preferentially tuned to satiety state (22, 33). Because subjects in our study were fed to satiety before testing, we suspect that the absence of activation of the OFC is related to sensory-specific satiety effects. Finally, a recent study (34) suggests that top-down input, such as a focus on intensity or pleasantness, can bias how a population of insula or OFC neurons responds to a sensory signal. In this study, subjects were simply asked to taste sweet solutions and not given any specific instruction regarding a focus on intensity or pleasantness of sweet taste.

Selection of sucralose as a contrast solution

Several factors played a role in our consideration of a "contrast" taste solution for sucrose. First, studies have shown that water and sugar have a similar anterior insula neural response (22, 27, 35), and does not differentiate women recovered from anorexia nervosa and control women (9). Second, it is well known that women with anorexia and bulimia nervosa have strong emotional responses to high calorie foods. Moreover, some but not all studies suggest women with anorexia and bulimia nervosa have altered sensing of sweet tastes compared to healthy control women (36). Thus, in order to control for sweet taste and effectively measure the response to caloric stimuli, we contrasted the artificial sweetener Splenda® (sucralose) to sucrose. On the day before the fMRI study, each subject was tested in order to identify a sucralose solution that was matched to the sweetness of the sucrose solution for that individual. This design has the potential to distinguish whether there was an altered response to processing of sucrose molecules while controlling for the sweet taste. In order to control for delivery, we used a pump apparatus to deliver repeated 1 cc doses of sucrose or sucralose solutions. We used a 10% sucrose solution, which is a level of sweetness preferred by the general public and present in soft drinks (9), and we used sucralose as the artificial sweetener because it tastes and is molecularly similar to sugar but lacks the caloric properties of sugar (37).

The use of recovered versus clinically ill subjects

The study of eating disorders raises several questions regarding cause and consequence. Do neurobiological disturbances cause pathological eating behaviors? Or, are neurobiological disturbances secondary to abnormal nutrition? In order to avoid the confounding effects of altered nutritional state, we studied women recovered from anorexia and women recovered from bulimia nervosa. Approximately 50% to 70% of affected individuals will eventually have complete or moderate resolution of restricting or binge behaviors, and weight and menses normalization (38). It is important to emphasize that core temperament and personality traits persist after recovery from both anorexia nervosa and bulimia nervosa

(39) and are similar to the symptoms described premorbidly in childhood (40). As such, they may be traits related to underlying genetic vulnerabilities. Even if persistent psychophysiological disturbances in recovered eating disorders are “scars,” they are still likely to help understand the processes contributing to these disorders.

The identification of effective treatments that reverse the symptoms of anorexia nervosa and bulimia nervosa has been elusive. Anorexia nervosa is a disorder of considerable morbidity and mortality (41) for which there are no proven, FDA approved treatments. Moreover, while medication and psychotherapies diminish symptoms in bulimia nervosa, most individuals remain symptomatic (42). An understanding of the physiology underlying disturbances of appetitive behaviors may accelerate the development of better treatments for anorexia nervosa and bulimia nervosa.

TABLE S1. Characterization of a priori regions of interest (ROI) that were used to mask the whole brain analysis. Cluster size is given in terms of both volume (mm^3) and number of voxels (#). Talairach XYZ coordinates indicate center of mass. The minimum cluster size in number of voxels is provided for each ROI for each p value that is used in the analysis. Calculations are based on AlphaSim. Brodmann’s area (BA).

mm^3	#	X	Y	Z	Region	BA	Minimum cluster at p<		
							0.05	0.01	0.005
11008	172	-1	36	-19	Left Rectal Gyrus	11	448	320	256
18112	283	0	32	5	Right Anterior Cingulate	24	512	320	320
6592	103	43	29	24	Right Middle Frontal Gyrus	46	384	256	256
7296	114	-41	28	24	Left Middle Frontal Gyrus	46	384	256	256
2112	33	9	12	-1	Right Caudate		192	192	192
2176	34	-9	11	-1	Left Caudate		192	192	128
2176	34	11	9	13	Right Caudate		192	192	128
2176	34	-11	8	13	Left Caudate		192	192	128
15232	238	40	-7	10	Right Insula	13	512	320	320
14720	230	-39	-7	10	Left Insula	13	512	320	320
46784	731	1	-11	34	Right Dorsal Cingulate Gyrus	24	768	448	384
768	12	8	-17	-10	Right Substantia Nigra		128	128	128
768	12	-8	-17	-10	Left Substantia Nigra		128	128	128
7040	110	13	-18	8	Right Thalamus		448	256	256
6848	107	-13	-19	8	Left Thalamus		384	256	256

TABLE S2. Significant clusters of activation within each group (control women / women recovered from anorexia nervosa / women recovered from bulimia nervosa) and each condition (sucrose / sucralose) for the group by condition interaction. The whole brain analysis was performed to investigate what regions outside of the regions of interest showed activation. 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 is the control women group. However these regions were often highly significant and created non-specific clusters, such as the sucralose activation in the recovered bulimic group that spread across the bilateral insula. For these reasons the ROI analysis is presented in the manuscript as primary activation. Volume (mm^3). Number of voxels (#). Brodmann's area (BA).

Contrast	mm^3	#	X	Y	Z	Region	BA	T-value
Control women: Sucrose								
	62784	981	47	-13	21	Right Insula	13	5.51
	59200	925	-44	-13	21	Left Insula	13	5.47
	21376	334	3	-1	50	Medial Frontal Gyrus	6	5.29
	10752	168	-4	-63	-16	Left Cerebellum		4.84
Control women: Sucralose								
	27520	430	48	-7	18	Right Insula	6	5.35
	26944	421	-46	-11	24	Left Insula	6	5.14
	5056	79	4	0	49	Right Medial Frontal Gyrus	6	4.87
	4992	78	45	-36	34	Right Supramarginal Gyrus	40	5.12
	2752	43	4	-65	50	Right Precuneus	7	4.92
Women recovered from anorexia nervosa: Sucrose								
	16640	260	51	-11	23	Right Insula	13	5.02
	15872	248	-49	-12	22	Left Insula	13	5.21
	4352	68	25	-63	-23	Right Culmen		4.74
	3328	52	13	-19	10	Right Thalamus		4.89
	2752	43	-23	-62	-23	Left Culmen		4.98
	2304	36	-16	-13	6	Left Thalamus		4.96
Women recovered from anorexia nervosa: Sucralose								
	12608	197	-50	-13	21	Left Insula	13	5.15
	10432	163	52	-10	20	Right Insula	13	4.97
Women recovered from bulimia nervosa: Sucrose								
	62784	981	47	-13	21	Right Insula	13	5.51
	59200	925	-44	-13	21	Left Insula	13	5.47
	21376	334	3	-1	50	Medial Frontal Gyrus	6	5.29
	10752	168	-4	-63	-16	Left Cerebellum		4.84
Women recovered from bulimia nervosa: Sucralose								
	95104	1486	2	-11	24	Cingulate Gyrus + bilateral insula	24+13	5.15
	3200	50	-16	-57	-22	Left Cerebellum		4.74
	2368	37	3	-65	46	Right Precuneus	7	4.81
Group by Condition								
	27840	435	-4	-56	46	Left Precuneus	7	4.36

14528	227	48	-25	22	Right Inferior Parietal Lobule	13	4.61
13568	212	-43	-8	31	Left Precentral Gyrus	6	4.61
5184	81	8	2	54	Right Medial Frontal Gyrus	6	4.35
4224	66	-50	-53	4	Left Middle Temporal Gyrus	37	4.01
3712	58	39	-63	36	Right Precuneus	39	4.05
3328	52	40	9	1	Right Insula	13	4.33
2752	43	49	-46	-5	Right Brodmann area 37	37	4.38
2176	34	41	-88	2	Right Middle Occipital Gyrus	18	4.15
2048	32	51	-13	-7	Right Middle Temporal Gyrus	22	4.47
2048	32	-14	-30	5	Left Thalamus	27	4.37

TABLE S3. Correlations comparing groups, clinical characteristics, condition, and ROI. The Temperament and Character Inventory (TCI) to assess harm avoidance (HA), and the State-Trait Anxiety Inventory Y (STAI-Y) to assess state and trait anxiety were correlated with brain activation in Control Women (CW), women recovered from anorexia nervosa (RAN), and women recovered from bulimia nervosa (RBN). No correlations survived after controlling for multiple comparisons.

Group	Variable	Condition	Region	P	R^2	Direction
CW	Age	Sucrose	R Insula	0.012	0.418	-
CW	Age	Sucralose	R Cingulate Gyrus	0.010	0.437	-
CW	Age	Sucralose	R Insula	0.037	0.314	-
CW	Age	Sucralose	L Insula	0.021	0.369	-
CW	BMI	Sucrose	R Insula	0.033	0.414	-
CW	BMI	Sucrose	L Insula	0.042	0.385	-
CW	BMI	Sucralose	R Thalamus	0.026	0.440	-
CW	BMI	Sucralose	L Thalamus	0.050	0.362	-
CW	BMI	Sucralose	R Cingulate Gyrus	0.017	0.484	-
CW	BMI	Sucralose	R Midbrain	0.026	0.440	-
CW	STAIY-S	Sucrose	L Insula	0.025	0.353	+
CW	STAIY-S	Sucralose	R Cingulate Gyrus	0.040	0.307	+
CW	STAIY-S	Sucralose	L Insula	0.025	0.355	+
CW	STAIY-T	Sucrose	L Insula	0.024	0.355	+
CW	STAIY-T	Sucralose	R Cingulate Gyrus	0.012	0.418	+
CW	STAIY-T	Sucralose	L Insula	0.047	0.291	+
CW	STAIY-T	Sucralose	R Thalamus	0.031	0.333	+
CW	STAIY-T	Sucralose	L Thalamus	0.006	0.480	+
RAN	HA	Sucrose	L Insula	0.035	0.319	+
RBN	Age	Sucrose	L Caudate	0.014	0.385	+
RBN	Age	Sucrose	R Middle Frontal Gyrus	0.012	0.396	+
RBN	Age	Sucralose	L Thalamus	0.012	0.394	+
RBN	Age	Sucralose	R Midbrain	0.006	0.448	+
RBN	BMI	Sucrose	R Thalamus	0.026	0.350	-
RBN	BMI	Sucralose	L Thalamus	0.022	0.365	-
RBN	BMI	Sucralose	R Thalamus	0.010	0.440	-
RBN	HA	Sucrose	R Cingulate Gyrus	0.018	0.363	-
RBN	HA	Sucrose	L Thalamus	0.017	0.364	-
RBN	HA	Sucrose	L Caudate	0.006	0.457	-
RBN	HA	Sucrose	R Middle Frontal Gyrus	0.033	0.304	-

References

1. Drewnowski A, Halmi KA, Pierce B, Gibbs J, Smith GP. Taste and eating disorders. Am J Clin Nutr. 1987;46(3):442-50.
2. Garfinkel P, Moldofsky H, Garner DM. The stability of perceptual disturbances in anorexia nervosa. Psychol Med. 1979;9(4):703-8.
3. Simon Y, Bellisle F, Monneuse MO, Samuel-Lajeunesse B, Drewnowski A. Taste responsiveness in anorexia nervosa. British Journal of Psychiatry. 1993;162:244-6.
4. Klein D, Schenbendach J, Brown A, Smith G, Walsh B. Modified sham feeding of sweet solutions in women with and without bulimia nervosa. Physiol Behav. 2009;96(1):44-50.
5. 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.
6. Moskowitz H. The sweetness and pleasantness of sugars. Am J Psychol. 1971;84:387-405.
7. Sunday S, Einhorn A, Halmi K. Relationship of perceived macronutrient and caloric content to affective cognitions about food in eating-disordered, restrained, and unrestrained subjects. Am J Clin Nutr. 1992;55:362-71.
8. Frank G, Kaye W, Carter C, Brooks S, May C, Fissel K, Stenger V. The evaluation of brain activity in response to taste stimuli--a pilot study and method for central taste activation as assessed by event related fMRI. J Neurosci Methods. 2003;131(1-2):99-105.
9. 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.
10. Sunday SR, Halmi KA. Taste perceptions and hedonics in eating disorders. Physiol Behav. 1990;48(5):587-94.
11. Szalay C, Abraham I, Papp S, Takacs G, Lukats B, Gati A, Karadi Z. Taste reactivity deficit in anorexia nervosa. Psychiatry Clin Neurosci. 2010;64(4):403-7.
12. Goldzak-Kunik G, Griedman R, Spitz M, Sandler L, Leshem M. Intact sensory function in anorexia nervosa. Am J Clin Nutr. 2012;95(2):272-82.
13. Craig A. How do you feel--now? The anterior insula and human awareness. Nature Rev Neuroscience. 2009;10(1):59-70.
14. Kaada BR, Jansen J, Andersen P. Stimulation of the hippocampus and medial cortical areas in unanesthetized cats. Neurology. 1953;3(11):844-57.
15. Carmichael ST, Clugnet MC, Price JL. Central olfactory connections in the macaque monkey. J Comp Neurol. 1994;346(3):403-34.
16. Mesulam MM, Mufson EJ. Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. J Comp Neurol. 1982;212(1):1-22.
17. 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.
18. 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.
19. 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.
20. 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.
21. Frank G, Reynolds J, Shott M, O'Reilly R. Altered temporal difference learning in bulimia nervosa. Biol Psych. 2011;70(8):728-35.
22. Rolls ET. Taste, olfactory, and food texture processing in the brain, and the control of food intake. Physiol Behav. 2005;85(1):45-56.
23. O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G. Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport. 2000;11(4):893-7.
24. Kringelbach ML, O'Doherty J, Rolls E, Andrews C. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex. 2003;13:1064-71.
25. Balleine B, Dickinson A. The effect of lesions of the insular cortex on instrumental conditioning evidence for a role in incentive memory. J Neurosci Methods. 2000;20(23):8954-64.

26. Dunn L, Everitt B. Double dissociations of the effects of amygdala and insular cortex lesions on conditioned taste aversion, passive avoidance, and neophobia in the rat using excitotoxin ibotenic acid. Behav Neurosci. 1988;102(1):3-23.
27. Small D, Zatorre R, Dagher A, Evans A, Jones-Gotman M. Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain. 2001;124(9):1720-33.
28. Kazama A, Bachevalier J. Selective aspiration of neurotoxic lesions of the orbitofrontal areas 11 and 13 spared monkeys' performance on the object reversal discrimination task. Soc Neurosci Abstr. 2006;32:670.25.
29. Critchley H, Rolls E. Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. J Neurophysiol. 1996;75:1673-86.
30. Hikosaka K, Watanabe M. Delay activity of orbital and lateral prefrontal neurons of the monkey varying with different rewards. Cereb Cortex. 2000;10(3):263-71.
31. Gottfried J, O'Doherty J, Dolan R. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science. 2003;301(5636):1104-7.
32. 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.
33. Rolls B, Rolls E, Rowe E, Sweeney K. Sensory specific satiety in man. Physiol Behav. 1981;27:137-42.
34. Grabenhorst F, Rolls E, Bilderbeck A. How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices. Cereb Cortex. 2008;18(7):1549-59.
35. De Araujo I, Rolls E, Kringelbach M, McGlone F, Phillips N. Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. Eur Journal of Neuroscience. 2003;18:2059-68.
36. Drewnowski A. Taste responsiveness in eating disorders. Ann NY Acad Sci. 1989;575:399-408.
37. Knight I. The development and applications of sucralose, a new high-intensity sweetener. Can J Physiol Pharmacol. 1994;72:435-9.
38. Kaye W, Fudge J, Paulus M. New insight into symptoms and neurocircuit function of anorexia nervosa. Nat Rev Neurosci. 2009;10(8):573-84.
39. Wagner A, Greer P, Bailer U, Frank G, Henry S, Putnam K, Meltzer CC, Ziolko SK, Hoge J, McConaha C, Kaye WH. Normal brain tissue volumes after long-term recovery in anorexia and bulimia nervosa. Biological Psychiatry. 2006;59(3):291-3.
40. Lilenfeld L, Wonderlich S, Riso LP, Crosby R, Mitchell J. Eating disorders and personality: a methodological and empirical review. Clinical Psychology Review. 2006;26(3):299-320.
41. Sullivan PF. Mortality in anorexia nervosa. Am J Psychiatry. 1995;152(7):1073-4.
42. Walsh BT, Hadigan CM, Devlin MJ, Gladis M, Roose SP. Long-term outcome of antidepressant treatment for bulimia nervosa. Am J Psychiatry. 1991;148(9):1206-12.