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## Orbitofrontal Cortex Volume and Brain Reward Response in Obesity

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### Abstract

**Background/Objectives**—What drives overconsumption of food is poorly understood.

Alterations in brain structure and function could contribute to increased food seeking. Recently brain orbitofrontal cortex volume has been implicated in dysregulated eating but little is known how brain structure relates to function.

**Subjects/Methods**—We examined obese (n=18, age=28.7.4±8.3 years) and healthy control women (n=24, age=27.4±6.3 years) using a multimodal brain imaging approach. We applied magnetic resonance and diffusion tensor imaging to study brain gray and white matter volume as well as white matter integrity, and tested whether orbitofrontal cortex volume predicts brain reward circuitry activation in a taste reinforcement-learning paradigm that has been associated with dopamine function.

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### Conflicts of Interests Statement

The authors declare no conflicts of interest.

All authors contributed significantly to this manuscript.

**Results**—Obese individuals displayed lower gray and associated white matter volumes ( $p < .05$  family wise error (FWE)-small volume corrected) compared to controls in the orbitofrontal cortex, striatum, and insula. White matter integrity was reduced in obese individuals in fiber tracts including the external capsule, corona radiata, sagittal stratum, and the uncinate, inferior fronto-occipital, and inferior longitudinal fasciculi. Gray matter volume of the gyrus rectus at the medial edge of the orbitofrontal cortex predicted functional taste reward-learning response in frontal cortex, insula, basal ganglia, amygdala, hypothalamus and anterior cingulate cortex in control but not obese individuals.

**Conclusions**—This study indicates a strong association between medial orbitofrontal cortex volume and taste reinforcement-learning activation in the brain in control but not in obese women. Lower brain volumes in the orbitofrontal cortex and other brain regions associated with taste reward function as well as lower integrity of connecting pathways in obesity may support a more widespread disruption of reward pathways. The medial orbitofrontal cortex is an important structure in the termination of food intake and disturbances in this and related structures could contribute to overconsumption of food in obesity.

### Keywords

Obesity; Gray Matter; White Matter; Reward; DTI; VBM; Orbitofrontal; SPSRQ

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### Introduction

With more than a third of the US population obese<sup>1</sup> (defined as body mass index, BMI, of  $30 \text{ kg/m}^2$ ), understanding the neurobiology of disturbed eating behaviors is of significant importance. What, when and how much we eat is influenced, at least in part, by brain circuits involving taste perception and afferents to motivational and hedonic pathways,<sup>2</sup> which likely play an important role in obesity (OB).<sup>3</sup> In recent years, it has further been suggested that individuals prone to OB and aberrant eating behaviors could get ‘addicted’ to food, as the same neural pathways that reinforce natural appetitive behaviors are also activated in response to addictive drugs.<sup>4, 5</sup>

The networks processing taste and taste-reward are complex. After taste stimulation in the mouth, neurons project via brainstem and thalamus to the primary taste cortex, comprised of the insula, and from there to the ventral striatum, amygdala, hypothalamus, and orbitofrontal cortex (OFC).<sup>6</sup> Within that circuitry, the brain neurotransmitter dopamine is associated with the motivational aspect of approaching foods and provides a learning signal in response to cues that predict taste and other rewards.<sup>7</sup>

Food *restriction* and weight *loss* are associated with heightened dopamine-related brain reward response in rodents,<sup>8</sup> while *overconsumption* of food leads to addiction-like dopamine D2 receptor down-regulation in the striatum.<sup>9</sup> In line with those findings are human functional imaging studies indicating a reduction in brain response to food receipt in OFC and striatum in OB.<sup>10</sup> In addition, our group<sup>11</sup> recently found OB displayed diminished brain response during a dopamine-related taste reward learning task in ventral striatum and insula. In that task subjects learn to predict taste stimuli in response to conditioned visual cues but when a taste stimulus is received or omitted unexpectedly then this “prediction

error” is associated with activation or depression of dopamine neuronal activity.<sup>12</sup> In contrast, underweight individuals showed increased brain response in this task,<sup>11</sup> further supporting the idea that over- and underweight states may be associated with opposite brain alterations. Other brain research in OB, summarized in a recent meta-analysis of functional magnetic resonance imaging studies that used visual food stimuli provided evidence that OB is associated with increased brain response in brain regions that evaluate potentially rewarding stimuli such as the prefrontal cortex, but decreased activation in areas involved in cognitive control and interoceptive awareness including the insula and dorsolateral prefrontal cortex.<sup>13</sup>

Altered brain gray (GM) and white matter (WM) structure might be directly related to altered brain function and behavior,<sup>14</sup> however previous research in OB has been inconsistent, finding both increases and decreases in brain volume being associated with higher BMI and OB in frontal, temporal, and limbic brain regions.<sup>15, 16</sup>

Most recently, we found in individuals with the eating disorders anorexia (AN) and bulimia (BN) nervosa increased gray matter volume in the gyrus rectus across age groups and different illness states.<sup>17, 18</sup> The gyrus rectus is the medial part of the OFC and has been associated with value attribution to food stimuli, taste pleasantness, and food avoidance.<sup>19</sup> Thus, the gyrus rectus could also be a key component in the pathophysiology of OB. We had previously hypothesized that increased gyrus rectus volume could contribute to early satiation and chronic or episodic food restriction in AN or BN.<sup>17</sup> In contrast, in OB, gyrus rectus volumes might be smaller compared to controls, and thus making it more difficult for individuals with OB to terminate food intake.

In addition to measurement of GM and WM *volume*, magnetic resonance imaging allows to study integrity of brain WM tracts by mapping water diffusivity in WM structures.<sup>20</sup> Diffusivity can be measured as fractional anisotropy (FA) along WM axons related to axon myelination and density, as well as the apparent diffusion coefficient (ADC), assessing water diffusivity at the voxel level. Higher FA is related to better myelination, whereas higher ADC indicates dispersed water diffusion reflecting cell damage.<sup>20</sup> Few studies have employed this method in OB, showing higher BMI associated with lower WM integrity in fornix and corpus callosum,<sup>21</sup> or decreased WM integrity in corticospinal tracts, mammillary bodies and corpus callosum.<sup>22</sup>

In summary, studies suggest both structural and functional GM and WM alterations in OB, but the studies have been inhomogeneous. What is especially missing in our understanding of brain function in OB is an integrated concept of how brain structure could mechanistically be involved in brain function that drives food intake.

In the present study we explored reward circuitry by measuring brain GM and WM volume together with WM integrity in OB compared to healthy control women, and examined directly potential interactions between brain volume and reward prediction response from a dopamine associated reward learning paradigm that we reported before.<sup>11</sup> Testing such an interaction has not been reported previously. Our primary hypothesis was that OB would display reduced GM and associated WM volumes in the gyrus rectus. Additionally, we

hypothesized that gyrus rectus volume might be directly related to normal brain taste reward learning response, as it computes reward values, responds to the amount of food eaten and controls how much we eat,<sup>23, 24</sup> but that this relationship would be disturbed in OB.

## Subjects and Methods

### Participants

Forty-two right-handed healthy women similar in age participated, 18 obese (OB) and 24 normal weight controls. All imaging procedures occurred during the first 10 days of the follicular phase of the menstrual cycle.

### Screening and Study Inclusion

Participants were recruited through local advertisements in the Denver/Metro area. After complete description of study procedures, written informed consent was obtained. The Colorado Multiple Institutional Review Board approved all research procedures. Controls had a lifetime history of healthy body weight (between 90% and 110% of ideal body weight since menarche), no eating or weight concerns, and were free from any lifetime major medical or psychiatric illness. OB had a BMI  $\geq 30$ . Individuals taking any medication other than oral contraceptives were excluded.

Study participants completed: 1. Eating Disorder Inventory-3 (EDI-3) for Drive for Thinness, Bulimia, and Body Dissatisfaction.<sup>25</sup> 2. Temperament and Character Inventory (TCI) for Novelty Seeking, Reward Dependence and Harm Avoidance.<sup>26</sup> 3. Spielberger State and Trait Anxiety Inventory (STAI).<sup>27</sup> 4. Beck Depression Inventory (BDI).<sup>28</sup> 5. Revised Sensitivity to Punishment and Reward Questionnaire (SPSRQ).<sup>29</sup>

### Imaging Procedures

**MRI Acquisition for Brain GM and WM Volumes**—Structural brain images were acquired on a GE Signa 3T scanner, using an axial three-dimensional (3D) T1-weighted magnetization-prepared rapid acquisition gradient echo (IR-prepped fast spoiled gradient recall, FSPGR, field of view 22 cm, flip angle 10°, slice thickness 1.2 mm, scan matrix 256×256, TR/TE/TI= 10/3/450 ms, ASSET, 1 NEX, voxel size 0.89 mm<sup>3</sup>).

**MRI Acquisition for Functional Imaging**—Brain images were acquired on a GE Signa 3T scanner for blood oxygen dependent (BOLD) T2\* weighted echo-planar imaging (EPI), voxel size 3.4 × 3.4 × 2.6mm, TR 2100ms, TE 30ms, angle 70°, 30 slices, interleaved acquisition, 2.6mm slice thickness with 1.4mm gap.

**MRI Acquisition for Diffusion Tensor Imaging (DTI)**—Diffusion-weighted images (DWI) for DTI mapping included 25 DWI diffusion directions and one T2-weighted (b=0) baseline image. Each image included 45 slices acquired in axial anterior-posterior commissure orientation (128×128 matrix, TR/TE=16000/82.6 ms, field of view = 26 cm, b-value=1000, ASSET, slice thickness/gap = 2.6/0 mm).

**Functional Imaging Taste Reward Paradigm**—Subjects completed a fMRI taste reward conditioning task described previously,<sup>11</sup> learning the association between conditioned visual (CS) and unconditioned taste stimuli (US) and unexpected violation of those learned associations. This violation elicits the so-called prediction error, which has been associated with activation or depression of brain dopamine reward circuits.

Each participant's individual prediction error signal was modeled based on trial sequence. The predicted value ( $\hat{V}$ ) at any time ( $t$ ) within a trial is calculated as a linear product of weights ( $w_i$ ) and the presence of the conditioned visual stimuli (CS) at time  $t$ , coded in a stimulus representation vector  $x_i(t)$  where each stimulus  $x_i$  is represented separately at each moment in time:

$$\hat{V}(t) = \sum_i w_i x_i(t).$$

The predicted stimulus value at each time point  $t$  in the trial is updated by comparing the predicted value at time  $t+1$  to that actually observed at time  $t$ , leading to the prediction error  $\delta(t)$ :

$$\delta(t) = r(t) + \gamma \hat{V}(t+1) - \hat{V}(t)$$

where  $r(t)$  is the reward at time  $t$ . The parameter  $\gamma$  is a discount factor, which determines the extent to which rewards arriving sooner are more important than rewards that arrive later during the task, with  $\gamma=0.99$ . The weights  $w_i$  relate to how likely a particular unconditioned taste stimuli (US) follows the associated CS and are updated on each trial according to the correlation between prediction error and the stimulus representation:

$$\Delta w_i = \alpha \sum_t x_i(t) \delta(t)$$

where  $\alpha$  is a learning rate. Among various learning rates (0.2, 0.5, 0.7) a slow  $\alpha=0.7$  was the best fit for study groups. The initial reward values were 1 for Sucrose and 0 for No solution. The trial-to-trial prediction error was regressed with brain activation across all trials within each subject. For more detailed methods see Frank et al 2012.<sup>11</sup>

### GM and WM Analysis using Voxel Based Morphometry (VBM)

Pre-processing of T1-weighted images was performed using SPM8 VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/download/>) in Matlab R2009b, 7.9.0 (MathWorks, Natick, MA, USA). Images were normalized to MNI space using high-dimensional diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL),<sup>30</sup> using a custom template to normalize images based off individual brain images rather than a common template. Non-linear modulation was used, which produces template aligned tissue class images, but multiplies voxel values by non-linear components only, correcting volumes for individual brain sizes directly to the data instead of to the statistical model, thus reducing

distortions.<sup>31, 32</sup> Images were smoothed to an 8-mm full-width at half maximum Gaussian kernel.

### DTI Image Analysis

DTI datasets were processed using NordicICE 2.3.12 MRI toolbox (<http://www.nordicneurolab.com>) for 3-dimensional axonal fiber tracking using “Fiber Assignment by Continuous Tacking” (FACT).<sup>33</sup> Fibers are tracked continuously based on water diffusion. Where the tract leaves the voxel and enters the next, the direction is changed to that of the neighboring voxel. Exhaustive search tracking and a principal eigenvector angle stopping threshold of 41° was used, minimum fiber length 5 mm with only fractional anisotropy values greater than 0.2.<sup>33, 34</sup>

Whole brain FA and ADC maps were normalized to the average age-specific T1 template, smoothed with a 6-mm FWHM filter and masked with a WM mask and compared across groups using SPM8.

To delineate the WM pathways associated with clusters of significant FA groups difference, we applied probabilistic tractography using the Oxford Centre for Functional MRI of the Brain, (FMRIB) Diffusion Toolbox 4.1.3 (<http://www.fmrib.ox.ac.uk/fsl>) for preprocessing and PROBTRACKX toolbox for tractography<sup>35</sup> using default parameters of 5000 samples, 0.2 curvature threshold, and loopcheck options applied. From each individual’s path distribution estimation, a mean image was created using *fslmaths* toolbox.

### Statistical Analyses

**GM and WM Volume Differences**—A general linear model (GLM) whole-brain analysis was used (SPM8), a factorial design modeled with diagnosis as 2-level factor (controls and OB) and depression scores and total intracranial volume (TIV) as covariates. Initially, a voxel-wise F-test was performed,  $p < 0.001$  uncorrected, extent threshold  $> 50$  voxels. Results were corrected using SPM8 anatomical automatic labeling (AAL) atlas derived *a priori* defined anatomical regions involved in taste and reward processing (OFC, amygdala, ACC, insula, operculum, caudate, putamen, nucleus accumbens, pallidum, hippocampus, thalamus, hypothalamus, and midbrain), family-wise error (FWE) corrected at  $p < 0.05$ , and regional volumes that reached significance were extracted.<sup>17, 18</sup>

**GM Volume and Reward Correlation Analysis**—Based on the areas of significant group difference in GM volume, we extracted GM volumes for those anatomical regions (amygdala, caudate, OFC, hippocampus, and ACC), and conducted a within-group (controls and OB separately) whole brain regression analysis between those GM volumes and taste-reward task brain response. Depression and TIV were used as covariates. A voxel-wise F-test was performed, and contrast maps were created with an initial threshold set at a  $p < 0.005$  uncorrected and 50 voxel threshold. Results were corrected using *a priori* defined anatomical regions (same as used for volumetric analyses), FWE-corrected at  $p < 0.05$ , and regional activation that reached significance was reported.

**DTI Analysis**—A GLM was used for group comparison similar to volumetric analyses. A voxel-wise F-test was performed; threshold set at a  $p < 0.05$  FWE-corrected and extent threshold  $> 5$  voxels. We used this threshold to be conservative as there are no anatomical regions whole brain activation that can be corrected to. For the resulting clusters, mean FA and ADC values were extracted using the SPM marsbar toolbox. The WM bundles identified as significantly different across groups were then identified by visual inspection using the ‘MRI Atlas of Human White Matter’<sup>36</sup> and ‘Dissecting the White Matter Tracts: Interactive Diffusion Tensor Imaging Teaching Atlas’ by Hutchins et al., an online atlas (<http://www.asnr2.org/neurographics>).

Demographic, behavioral and extracted brain data were analyzed using SPSS (IBM-SPSS, Chicago, IL) and independent-samples *t*-test. Linear regression analyses to test behavior–brain relationships were applied for age, BMI, and reward and punishment sensitivity. Significant correlations were corrected for the false discovery rate using the method proposed by Benjamini & Hochberg (1995).<sup>37</sup>

## Results

### Demographic and Behavioral Data (Table 1)

OB and healthy controls were similar in age. OB showed the expected higher BMI, as well as higher scores on Depression (but within normal limits), Drive for Thinness, Bulimia, Body Dissatisfaction, Punishment Sensitivity, and Harm Avoidance. State and Trait anxiety as well as Novelty Seeking and Reward Sensitivity were similar in both groups.

### GM and WM Volume Results (Table 2, Fig. 1)

Total GM and WM brain volume was similar between groups. OB displayed less total cerebral spinal fluid volume than controls.

Localized GM and associated WM volumes (expressed as ratio of GM or WM per voxel) were reduced in OB compared to controls in the amygdala, caudate, ACC, hippocampus, OFC, and insular WM. Neither GM nor WM volumes were greater in OB compared to controls in any brain region.

### GM Volume and Taste Reward Task Correlation Results (Table 3, Fig.2)

There was a significantly negative correlation between left and right gyrus rectus GM volume and reward response in controls in the ACC, amygdala, striatum, hypothalamus, hippocampus, rolandic operculum, and insula. There was a significantly negative correlation between gyrus rectus GM volume and rolandic operculum functional brain reward response in OB.

### DTI Results (Table 4, Fig. 1)

DTI FA was reduced in OB compared to controls in bilateral anterior corona radiata, superior corona radiata, sagittal stratum, and external capsule. DTI FA was not greater in OB compared to controls in any brain region. ADC was greater in OB compared to controls in the right sagittal stratum and left superior corona radiata. The fiber paths that connect



those brain regions, as determined by probabilistic tractography, included the inferior fronto-occipital fasciculus, superior longitudinal fasciculus, anterior thalamic radiation, and uncinate fasciculus.

### Demographic and Behavioral Correlation Results

**Controls**—WM volume was significantly positively correlated with age in the left insula ( $r=.542$ ,  $p<.043$ ;  $x=-44$ ,  $y=-3$ ,  $z=-9$ ) and right gyrus rectus ( $r=.573$ ,  $p<.017$ ;  $x=8$ ,  $y=29$ ,  $z=-15$ ).

FA was significantly negatively correlated with age in the right sagittal stratum ( $r=-.521$ ,  $p<.018$ ;  $x=50$ ,  $y=-44$ ,  $z=-4$ ) and with BMI in the right superior corona radiata ( $r=-.473$ ,  $p<.039$ ;  $x=42$ ,  $y=-20$ ,  $z=34$ ).

**OB**—GM volume was significantly negatively correlated with age in the right gyrus rectus ( $r=-.678$ ,  $p<.012$ ;  $x=17$ ,  $y=23$ ,  $z=-12$  and  $r=-.615$ ,  $p<.040$ ;  $x=6$ ,  $y=56$ ,  $z=-23$ ).

FA was significantly negatively correlated with age in the right anterior corona radiata ( $r=-.644$ ,  $p<.008$ ;  $x=20$ ,  $y=42$ ,  $z=-6$ ).

### Discussion

The present study indicates that OB is associated with decreases in GM and associated WM volumes in OFC, insula, amygdala, striatum, hippocampus, and ACC as well as decreased WM integrity in the corona radiata, sagittal stratum, and external capsule. Gyrus rectus GM volume predicted negatively brain activation during a reward learning paradigm in taste and reward-related regions including the insula, striatum, amygdala, hypothalamus and hippocampus in controls, but not OB, perhaps suggesting a potential mechanism that could alter reward function and eating regulation in OB.

As expected, OB showed higher BMI, and scored higher on body dissatisfaction, bulimic symptoms and drive for thinness. OB displayed greater SPSRQ<sup>29</sup> sensitivity to punishment than controls, similar to adults with AN and BN,<sup>38, 39</sup> suggesting increased sensitivity to negative reinforcement in OB.

### GM and Associated WM Volume

OB displayed lower regional GM and associated WM volume than controls in OFC, insula, caudate, amygdala, hippocampus and ACC, a network of regions that contributes to taste and reward processing,<sup>3</sup> as well as motivation, emotion processing and food intake control.<sup>24</sup> More specifically, the OFC regulates when to stop eating a particular food, the ACC is important in anticipating food reward,<sup>19, 40</sup> and the insula as the primary taste cortex processes taste quality,<sup>11</sup> but gets also activated in response to visual food stimuli<sup>13</sup> and has been associated with ‘craving’ or ‘wanting’ of rewards in drug addiction,<sup>41</sup> food-cravings,<sup>19</sup> and hunger.<sup>42</sup> The caudate receives direct input from the insula and is thought to regulate the incentive properties of food,<sup>3</sup> and in OB, activation in this region has been associated with food cravings and food reward anticipation.<sup>19, 43</sup> Importantly, the striatum including the caudate contains dopaminergic terminals from the midbrain that are involved in the



motivational aspect of food approach. The amygdala drive dopamine activation in the reward cycle,<sup>44</sup> and greater activation in OB has been implicated in studies involving visual food cues.<sup>19</sup> Altogether it is possible that reduced volumes in this circuitry may contribute to altered internal feedback mechanisms in response to food, leading to an inability to stop food intake when physiologically enough food would have been eaten.

### GM Volume and Reward Correlation Analysis

Importantly and novel in this study, we conducted a regression analysis between GM volume and brain response during a taste reward conditioning task.<sup>11</sup> This showed a negative structure-function relationship between gyrus rectus GM volume and brain reward activation in reward-related regions including the amygdala, caudate, putamen, insula, ACC, hippocampus, rolandic operculum and hypothalamus in controls, but not OB. In OB there was only a significantly negative association between gyrus rectus GM volume and taste reward response activation in the rolandic operculum.

The gyrus rectus is the medial part of the OFC and further defined by a caudal agranular and dysgranular layer (area 14) that transitions antero-superiorly into the granular layer (area 11).<sup>45</sup> The OFC is an important component of hedonic and motivational aspects of reward<sup>23</sup> and has been implicated in addiction.<sup>46</sup> The OFC is connected to all sensory modalities<sup>6</sup> and is integral in controlling reward- and punishment-related behavior.<sup>23</sup> The gyrus rectus' role in regulating sensory specific satiety has particular implication for obesity, as a dysfunction in this structure could contribute to overeating.<sup>47</sup> Little is known though whether connections of the OFC within the taste reward circuitry are in a positive or negative feedback fashion.

The current literature suggest that obese individuals have heightened brain response to visual food cues, but reduced brain satiety response.<sup>19</sup> Our results in the control group suggests that the larger the OFC volume the smaller brain response during reward learning as expressed by predication error response, which has not been shown before. Thus the OFC may regulate motivational pathways for food approach. In OB however, smaller OFC volume together with a lack of relationship of OFC volume and functional taste reward response suggests that a feedback mechanism between OFC and taste reward pathways is disturbed, which could interfere with healthy control of eating. It is unclear however, whether smaller gyrus rectus volume is a premorbid vulnerability for OB or whether it is adaptive to excessive food intake, for instance in response to inflammatory processes that have been associated with OB and could impact brain structure.<sup>48</sup>

The correlation between gyrus rectus volume and the rolandic operculum was preserved in OB. The rolandic operculum covers the superior posterior insula and has been implicated in somatosensory processing of taste stimuli.<sup>49-51</sup> One possible explanation for the preserved structure-function relationship between gyrus rectus GM volume and rolandic operculum in the obese group is that somatosensory processing of taste and somatic sensations involved in food intake remain intact, while the circuitry for integration of the rewarding aspects of taste may be disrupted.<sup>3</sup>

## WM Integrity

OB displayed reduced WM integrity (lower FA) in the external capsule, which lies between the putamen medially and claustrum laterally. The external capsule connects ventral and medial prefrontal cortices with limbic regions,<sup>52</sup> contains fibers from both the uncinate fasciculus and inferior fronto-occipital fasciculus, and connects the amygdala and hippocampus with prefrontal and OFC regions. Thus those pathways connect GM regions that showed reduced volume in OB in this study, and locally altered fiber connections between these regions may further suggest disruption of a larger taste reward circuitry.

Other WM tracts with reduced integrity were the sagittal stratum that conveys fibers from the parietal, occipital, cingulate, and temporal regions to the thalamus and contains the inferior longitudinal fasciculus, a long association system connecting visual pathways in the occipito-temporal cortices.<sup>52</sup> The corona radiata, a collection of fiber bundles that extend from the internal capsule to cerebral cortex,<sup>52</sup> basal ganglia and spinal cord, has been associated with central taste disorders.<sup>53</sup> In summary, OB displayed localized disrupted WM integrity in many fiber tracts that connect frontal and limbic regions of the brain. While speculative, it is possible that reduced integrity of WM tracts between OFC and limbic brain regions involved in reward processing may contribute to the lack of OFC volume-taste reward learning signal relationship in OB. Surprisingly, OB did not display decreases in fornix integrity as has been previously reported in OB<sup>21</sup> and other eating problems.<sup>18, 54, 55</sup> Differing results may be explained by differences in inclusion of age, depression, and gender, but this will require study in a larger sample.

A limitation is the potentially confounding effect from normalization of brain images to a template. In order to minimize such effects, our methods included a template that was based off the current study population, and a correction for individual brain sizes that was directly applied to the data instead of to the statistical model, thus reducing distortions.<sup>31, 32</sup> The present study is also limited to individuals who are already obese and so we cannot discern whether these differences are pre-morbid or are a result of the OB. Additionally, we examined brain structure and function only in female individuals and thus we cannot generalize the findings to males. Future studies are needed to address these concerns.

In summary, this multimodal imaging study is the first in OB research to study and integrate brain GM and associated WM volume, white matter connectivity, and functional response from a reward learning task that has been associated with dopaminergic pathways. Importantly we find in OB a pattern of GM volume reduction across the taste reward system. Gyrus rectus GM volume predicted reward learning response in controls, but not OB, suggesting a disrupted pathway between the OFC and its associated connections in OB. This finding is further supported by the reduction in WM integrity in OB in fiber tracts that connect frontal with limbic and subcortical brain regions, which could further contribute to disturbed reward circuitry feedback. Whether the alterations found exist premorbidly or whether these are alterations in response to specific eating patterns need further study.

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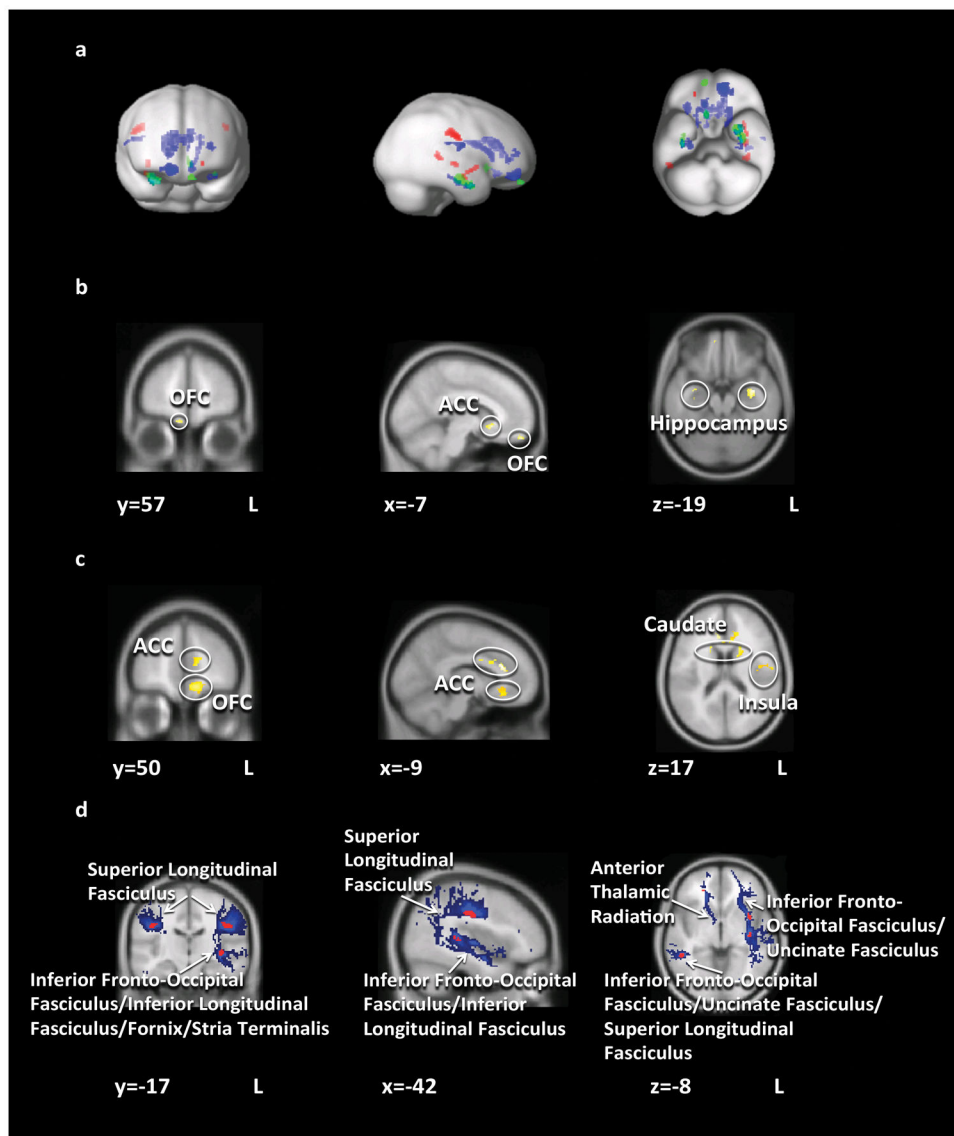
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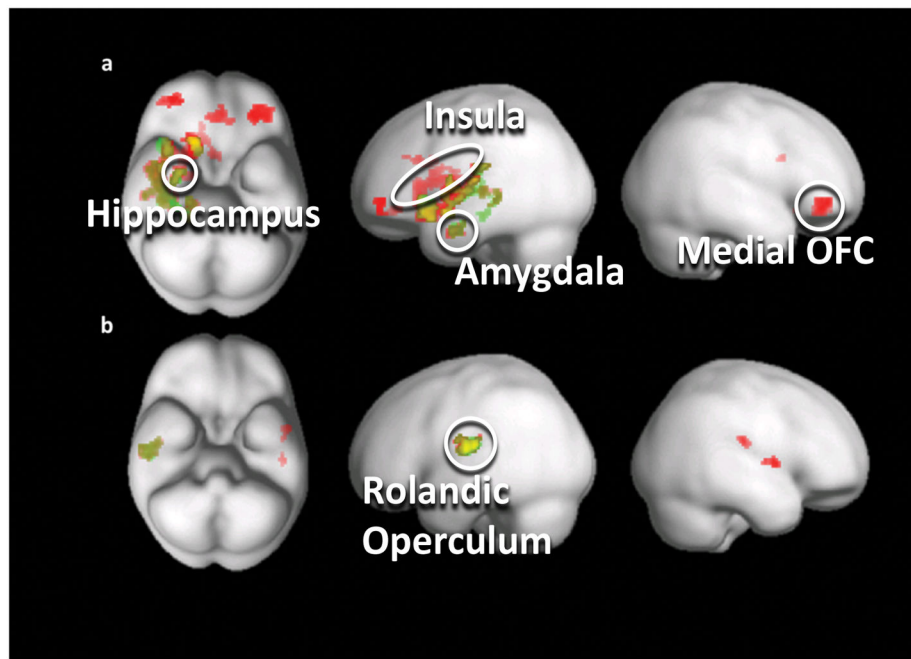
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**Figure 1.** Structural brain results. a) Areas of significant gray matter volume (green), white matter volume (blue), and white matter integrity (red) differences b) Gray matter volume Control Women > Obese Women; c) White matter volume Control Women > Obese Women; d) Areas of significant FA difference (red, Control Women > Obese Women) overlaid on mean group probabilistic tractography path distribution estimations (blue). Abbreviations: OFC = orbitofrontal cortex; ACC = anterior cingulate cortex.





**Figure 2.** Gray matter volume and reward correlation analysis results. Significantly negative correlation between gyrus rectus right (red) and gyrus rectus left (green) gray matter volume and reward response in a) control women and b) obese women. Abbreviations: OFC = orbitofrontal cortex.



**Table 1**

Demographic variables for healthy control women and obese women.

	Control Women, n=24		Obese Women, n=18		t	p
	Mean	S.D.	Mean	S.D.		
Age (Years)	27.42	6.28	28.67	8.30	-0.56	0.581
Body Mass Index (kg/m <sup>2</sup> )	21.64	1.26	34.78	4.44	-12.18	<0.001
Harm Avoidance	9.58	3.99	12.61	4.91	-2.20	0.033
Novelty Seeking	17.92	5.16	20.94	5.29	-1.86	0.070
Reward Dependence	16.96	3.71	16.67	3.60	0.26	0.800
Depression (BDI)	1.13	0.95	4.67	4.78	-3.10	0.006
Drive for thinness (EDI-3)	2.63	3.41	11.67	7.35	-4.84	<0.001
Body Dissatisfaction (EDI-3)	4.38	4.25	26.17	9.04	-9.47	<0.001
Bulimia (EDI-3)	0.79	1.22	10.22	11.28	-3.53	0.003
Punishment Sensitivity	4.04	1.85	6.78	4.29	-2.53	0.019
Reward Sensitivity	4.42	2.84	6.22	4.49	-1.59	0.119
State Anxiety	32.67	11.79	36.78	13.84	-1.04	0.305
Trait Anxiety	33.92	11.35	39.44	11.16	-1.57	0.124

Whole brain and regional gray and white matter brain volumes across groups. Values for regional brain volumes are fractions of respective tissue type per volume.

Table 2

Whole Brain Volumes	Control Women, n=24		Obese Women, n=18		t	p
	Mean	SD	Mean	SD		
Gray Matter Volume (cm <sup>3</sup> )	629.65	62.12	627.98	51.13	0.09	0.926
White Matter Volume (cm <sup>3</sup> )	494.00	44.34	492.01	42.41	0.15	0.884
Cerebral Spinal Fluid Volume (cm <sup>3</sup> )	226.81	30.63	254.14	28.76	-2.94	0.005
Total Intracranial Volume (cm <sup>3</sup> )	1350.47	105.28	1374.13	100.49	-0.73	0.467
Anatomical Region	Cluster Size	p FWE-Corr	T/Z at peak	MNI Coordinates		
GM Volume Ratio				x	y	z
L Amygdala, BA 38	154	0.001	4.36/4.09	-26	5	-29
R Caudate	59	0.011	4.23/3.79	8	18	-9
R Superior Orbitofrontal Cortex, BA 11	38	0.008	4.39/3.91	9	56	-24
R Medial Orbitofrontal Cortex, Gyrus Rectus	4	0.017	3.98/3.61	17	23	-12
R Medial Orbitofrontal Cortex, Gyrus Rectus, BA 11	12	0.032	3.71/3.40	6	56	-23
R Anterior Cingulum, BA 32	2	0.033	3.91/3.55	6	20	-8
R Hippocampus	80	0.021	3.97/3.60	35	-13	-14
L Hippocampus	232	0.004	4.62/4.08	-36	-9	-18
WM Volume Ratio						
L Amygdala	63	0.003	4.26/3.82	-30	-4	-29
R Caudate	192	0.001	5.16/4.45	15	8	21
L Caudate	354	0.001	5.18/4.47	-15	8	19
R Medial Orbitofrontal Cortex	36	0.015	3.92/3.56	8	30	-14
L Medial Orbitofrontal Cortex	98	0.001	4.93/4.29	-12	50	-14
L Middle Orbitofrontal Cortex	3	0.021	3.93/3.57	-15	50	-18
L Superior Orbitofrontal Cortex	185	0.003	4.82/4.22	-14	48	-15
R Insula	135	0.005	4.78/4.19	30	27	12
R Insula, BA 13	22	0.045	3.87/3.52	38	-13	22
L Insula, BA 13	22	0.029	4.04/3.65	-36	-25	22

Whole Brain Volumes	Control Women, n =24		Obese Women, n =18		t	p
	Mean	SD	Mean	SD		
L Insula	7	0.049	3.81/3.48	-44	-3	-9
R Medial Orbitofrontal Cortex, Gyrus Rectus	29	0.030	3.71/3.40	8	29	-15
L Medial Orbitofrontal Cortex, Gyrus Rectus	97	0.001	4.93/4.30	-12	48	-15
R Anterior Cingulum	272	<0.001	6.00/4.98	9	29	22
R Anterior Cingulum	1	0.002	4.92/3.57	11	50	10
R Anterior Cingulum	24	0.011	4.35/3.89	11	47	4
R Anterior Cingulum	4	0.043	3.78/3.45	9	48	13
R Anterior Cingulum	53	0.048	3.73/3.42	11	32	-11
L Anterior Cingulum	437	0.002	5.01/4.35	-2	24	21
L Anterior Cingulum	70	0.002	5.03/4.36	-15	48	7
R Hippocampus	139	0.014	4.11/3.71	35	-15	-23
L Hippocampus	65	<0.001	5.46/4.64	-30	-12	-24
R Rolandic Operculum	11	0.042	3.66/3.36	38	-13	21
R Rolandic Operculum	21	0.006	4.46/3.96	44	-28	22
R Rolandic Operculum	11	0.019	3.66/3.36	45	-24	22
L Rolandic Operculum	179	0.019	4.08/3.68	-39	-24	22

Control Women > Obese Women; Whole-brain volumes represented as raw values. Regional brain volume contrasts based on group comparison corrected for total intracranial volume and depression. FWE-corr = family-wise error corrected; L = left; MNI = Montreal Neurological Institute; R = right.

Regions of significantly negative correlation between right and left gyrus rectus gray matter volume and taste reward activation in control and obese women.

Table 3

<b>Control Women</b>						
Anatomical Region	$k_E$	p	FWE-Corr	T/Z at peak	x	y z
<b><u>Right Gyrus Rectus</u></b>						
L Amygdala	26	0.036		3.74/3.22	-28	0 -24
L Caudate	238	0.023		4.68/3.80	-18	24 8
L Anterior Cingulum	59	0.023		4.81/3.88	-4	12 26
R Medial OFC	31	0.023		4.47/3.68	2	38 -10
L Medial OFC	17	0.024		4.54/3.72	0	38 -10
L Hippocampus	28	0.030		4.52/3.71	-22	-34 0
R Hypothalamus	3	0.007		3.86/3.29	8	-6 -8
L Insula	346	0.013		5.28/4.13	-42	2 -12
L Insula	26	0.017		5.16/4.07	-36	-22 22
L Putamen	91	0.037		4.42/3.65	-26	10 12
L Rolandic Operculum	52	0.002		6.25/4.60	-40	-20 22
<b><u>Left Gyrus Rectus</u></b>						
L Amygdala	23	0.043		3.64/3.15	-28	-2 -26
L Hippocampus	60	0.012		5.03/4.00	-22	-34 0
L Insula	116	0.030		4.83/3.89	-40	2 -14
L Rolandic Operculum	53	0.017		4.97/3.96	-40	-20 22
<b>Obese Women</b>						
<b><u>Right Gyrus Rectus</u></b>						
R Rolandic Operculum	17	0.003		7.48/4.48	50	-22 20
L Rolandic Operculum	155	0.039		5.71/3.90	-48	-10 14
<b><u>Left Gyrus Rectus</u></b>						
L Rolandic Operculum	164	0.030		5.91/3.97	-56	-20 16

**Table 4**

Regions of significant fractional anisotropy and apparent diffusion coefficient differences, Control Women > Obese Women.

Anatomical Region/Pathway	Cluster Size	p FWE-Corr	T/Z at peak	MINI Coordinates		
				x	y	z
<b>FA</b>						
R Anterior Corona Radiata - ATR/UF/IFOF	6	0.026	5.74/4.82	20	42	-6
R Superior Corona Radiata -SLF/IFOF/UF	30	0.003	6.57/5.31	42	-20	34
R Sagittal Stratum - IFOF/ILF	11	0.007	6.21/5.11	50	-44	-4
L External Capsule - UF/IFOF/SLF	18	0.006	6.29/5.15	-36	4	-8
L External Capsule - IFOF	15	0.013	6.01/4.99	-38	-16	-2
L Sagittal Stratum - IFO/ILF	19	0.01	6.11/5.05	-40	-34	6
L Sagittal Stratum - IFOF/ILF/FX/ST	7	0.025	5.76/4.84	-40	-6	-16
L Superior Corona Radiata - SLF	104	<0.001	8.21/6.16	-46	-16	30
<b>ADC</b>						
R Sagittal Stratum - IFOF/ILF	5	0.015	5.74/4.82	32	-52	-8
L Superior Corona Radiata - STR/CPT/CST	5	0.002	6.48/5.26	-18	-16	66

UF = uncinate fasciculus; IFOF = inferior fronto-occipital fasciculus; ATR = anterior thalamic radiation; SLF = superior longitudinal fasciculus; ILF = inferior longitudinal fasciculus; FX = fornix; ST = stria terminalis; STR = superior thalamic radiation; CPT = corticopontine tract; CST = corticospinal tract.