Importance of Reward and Prefrontal Circuitry in Hunger and Satiety: Prader-Willi Syndrome vs. Simple Obesity

Laura M. Holsen, Ph.D.[1,2], **Cary R. Savage, Ph.D.**[3,4,5], **Laura E. Martin, Ph.D.**[4,6], **Amanda S. Bruce, Ph.D.**[7], **Rebecca J. Lepping, M.A.**[4], **Eunice Ko, B.A.**[2], **William M. Brooks, Ph.D.**[4,8], **Merlin G. Butler, M.D., Ph.D.**[5], **Jennifer R. Zarcone, Ph.D.**[9], and **Jill M. Goldstein, Ph.D.**[1,2,10]

[1]Departments of Psychiatry and Medicine, Harvard Medical School, Boston, MA 02120

[2]Connors Center for Women's Health and Gender Biology, Division of Women's Health, Brigham 13 and Women's Hospital, Boston, MA 02120

[3]Center for Health Behavior Neuroscience, University of Kansas Medical Center, Kansas City, KS 66160

[4]Hoglund Brain Imaging Center, University of Kansas Medical Center, Kansas City, KS 66160

[5]Department of Psychiatry, University of Kansas Medical Center, Kansas City, KS 66160

[6]Department of Preventive Medicine and Public Health, University of Kansas Medical Center, Kansas City, KS 66160

[7]Department of Psychology, University of Missouri-Kansas City, Kansas City, MO 64110

[8]Department of Neurology, University of Kansas Medical Center, Kansas City, KS 66160

[9]Department of Pediatrics and Strong Center for Developmental Disabilities, University of Rochester Medical Center, Rochester, NY 14642

[10]Massachusetts General Hospital & Massachusetts Institute of Technology Athinoula Martinos Center for Biomedical Imaging, Charlestown, MA 02129

Abstract

Background—The majority of research on obesity has focused primarily on clinical features (eating behavior, adiposity measures), or peripheral appetite-regulatory peptides (leptin, ghrelin). However, recent functional neuroimaging studies have demonstrated that some reward circuitry regions which are associated with appetite-regulatory hormones are also involved in the development and maintenance of obesity. Prader-Willi syndrome (PWS), characterized by hyperphagia and hyperghrelinemia reflecting multi-system dysfunction in inhibitory and satiety mechanisms, serves as an extreme model of genetic obesity. Simple (non-PWS) obesity (OB) represents an obesity control state.

Corresponding Author: Laura M. Holsen, Ph.D., Brigham and Women's Hospital, Division of Women's Health, BC-3, 1620 Tremont St., Boston, MA 02120, Phone: (617) 525-8772, Fax: (617) 525-7746, lholsen@partners.org.

Objective—This study investigated subcortical food motivation circuitry and prefrontal inhibitory circuitry functioning in response to food stimuli before and after eating in individuals with PWS compared with OB. We hypothesized that groups would differ in limbic regions (i.e., hypothalamus, amygdala) and prefrontal regions associated with cognitive control [i.e., dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC)] after eating.

Design and Participants—Fourteen individuals with PWS, 14 BMI- and age-matched individuals with OB, and 15 age-matched healthy-weight controls (HWC) viewed food and non-food images while undergoing functional MRI before (pre-meal) and after (post-meal) eating. Using SPM8, group contrasts were tested for hypothesized regions: hypothalamus, nucleus accumbens (NAc), amygdala, hippocampus, OFC, medial PFC, and DLPFC.

Results—Compared with OB and HWC, PWS demonstrated higher activity in reward/limbic regions (NAc, amygdala) and lower activity in hypothalamus and hippocampus, in response to food (vs. non-food) images pre-meal. Post-meal, PWS exhibited higher subcortical activation (hypothalamus, amygdala, hippocampus) compared to OB and HWC. OB showed significantly higher activity versus PWS and HWC in cortical regions (DLPFC, OFC) associated with inhibitory control.

Conclusion—In PWS compared with obesity per se, results suggest *hyper*activations in subcortical reward circuitry and *hypo*activations in cortical inhibitory regions after eating, which provides evidence of neural substrates associated with variable abnormal food motivation phenotypes in PWS and simple obesity.

INTRODUCTION

In response to rising obesity rates, recent research has consistently identified brain circuitry involved in basic hunger and satiation and reward processing in obesity. Functional MRI (fMRI) studies comparing obese and healthy-weight individuals generally indicate hyperactivation in the amygdala[1], hippocampus[1,2], medial prefrontal cortex (mPFC)[1,3], anterior cingulate cortex[1,3], and insula[1,2] in response to food stimuli prior to eating, and in the hypothalamus[4] and mPFC[3] after eating. Hyperactivation in the striatum to food pictures in individuals with obesity has been documented[1,2,5], although *decreased* striatal activity in response to actual[6] and imagined[7] ingestion of rewarding (gustatory) food stimuli has been shown to be predictive of subsequent weight *gain* in women. Increasingly, fMRI studies focused on eating behaviors, weight gain, and obesity have highlighted dysfunction in regions involved in cognitive self-control and reward value coding, such as the dorsolateral prefrontal cortex (DLPFC)[8] and posterior orbitofrontal cortex (OFC)[9–12], respectively. Greater DLPFC activation was associated with higher levels of self-control during food-related decision-making in healthy-weight dieters[13] and in response to tasting a sweet rewarding food in healthy-weight and obese adolescent girls[14]. However, hyperactivation in DLPFC in response to food images was also reported in obese compared to healthy-weight children[10,15]. This suggests that for obese individuals, decision-making in the presence of

food stimuli, especially after eating, may require significantly greater top-down control from DLPFC to counteract hyperactivity of subcortical food reward circuitry. Few studies have examined whether the ability to recruit the DLPFC for inhibitory control of eating behavior is related to excessive overeating and weight outcomes in individuals with obesity.

Prader-Willi syndrome (PWS), characterized by extreme hyperphagia, obesity, and intellectual disability[16], is a contiguous gene syndrome affecting one in 20,000 live births[17] which results from the lack of expression of several imprinted genes in the 15q11-q13 region from the paternal chromosome 15, usually from a de novo deletion of this region or maternal disomy 15 (both 15s from the mother)[18]. Individuals with PWS display an insatiable appetite that, if left unchecked, leads to morbid obesity[16]. Consequences of unattended hyperphagia in PWS include maintenance of over 200% ideal body weight (in 1/3 of the PWS population) and occasional stomach rupture[19].

In contrast to simple obesity (OB; i.e., non-PWS obesity), the ratio of adiposity to lean mass is elevated[20,21] and total and resting energy expenditure decreased[22] in PWS. Although leptin levels are similar in PWS and OB[23], fasting ghrelin levels are over four times higher in PWS[24]. Individuals with PWS consume more[25] and eat for a longer period of time[25,26] than those with OB, suggesting possible disruption of basic satiety mechanisms. Additionally, higher-level cognitive control over eating behaviors ("hyperphagic drive") is disrupted in PWS and directly linked to extreme obesity[27], suggesting dysfunction in multiple processes involved in hunger, eating behavior, and weight gain in PWS.

Research into the neural substrates of hyperphagia has yielded important findings that parallel the behavioral phenotype in PWS. Although differences between individuals with PWS vs. healthy-weight controls have been observed during fasting[28,29], the most striking abnormalities in food reward circuitry appear following food intake. Post-meal hyperactivation in response to various food stimuli was reported in the hypothalamus[30], nucleus accumbens (NAc)[30], amygdala[29], hippocampus[29], medial PFC[29–31], OFC[29,32], and insula[29,30], providing evidence of dysfunction in reward circuitry implicated in satiety. However, most studies have employed small samples, examined either pre- *or* post-meal brain activation only, and made comparisons only to healthy-weight controls, limiting the interpretation of these PWS findings with regard to understanding the development of OB.

Collectively, previous studies on eating behavior, body composition, appetite-regulatory peptide levels, and neural substrates of hyperphagia in PWS indicate the potential of this genetic syndrome to serve as an extreme model of obesity. Despite a recent increase in functional neuroimaging studies on obesity and prefrontal inhibitory networks involved in dietary restraint, none compare OB and PWS. Our overarching hypothesis was that the absence of top-down control (operationalized as hypoactivation of DLPFC and posterior OFC) with hyperactivation of subcortical reward regions (hypothalamus, NAc, amygdala, hippocampus) may lead to phenotypic characteristics of hyperphagia and morbid obesity seen in PWS. The current study was designed to investigate subcortical food motivation circuitry and putative prefrontal inhibitory circuitry functioning in response to food stimuli before and after eating in a relatively large sample of individuals with PWS compared with

OB. We hypothesized that the most substantial differences between groups would be seen after eating in prefrontal regions associated with cognitive control.

SUBJECTS AND METHODS

Subjects

This study was approved by the Human Subjects Committees at the University of Kansas (KUMC) and University of Rochester (URMC) Medical Centers. Written informed consent was obtained from parents and assent was obtained from 14 individuals with Prader-Willi syndrome (PWS) (12 F/2 M; 2 Type 1 Deletion, 8 Type 2 Deletion, 4 UPD), 14 individuals with simple obesity (9 F/5 M; OB group), and 15 typically developing, healthy weight control subjects (9 F/6 M; HWC group). Diagnosis of PWS was confirmed through chromosomal and DNA molecular analysis as previously described[33]. Groups were made comparable on sex (Pearson Chi-Square; n.s.), age [mean age (in years) $\pm$ sd: PWS = 24.3 $\pm$ 11.3; OB = 25.0 $\pm$ 10.3; HWC = 23.1 $\pm$ 9.7; all t-tests n.s.] and handedness (all right-handed). The HWC group had a significantly lower BMI [mean BMI (in kg/m^2) $\pm$ sd = 21.2 $\pm$ 2.8] than both PWS (mean BMI = 32.1 $\pm$ 7.8; HWC vs. PWS: t = 4.96/p<0.01) and OB (mean BMI = 32.4 $\pm$ 3.5; HWC vs. OB: t = 9.57/p<0.01) groups. PWS and OB groups did not differ in BMI (t = 0.14, n.s.). IQ was measured in the PWS group only, and the group mean was representative for individuals with PWS (mean IQ $\pm$ sd = 67.4 $\pm$ 11.7).

Concomitant psychotropic medications in the PWS group included (number of subjects): buspirone (1), clonazepam (1), divalproex (2), escitalopram (1), fluoxetine (1), fluvoxamine (1), lorazepam (1), quetiapine (1), risperidone (1), topiramate (1), sertraline (1), and ziprasidone (1). One PWS participant was being treated for hypothyroidism. Seven PWS subjects were medication-free. All participants were free from current growth hormone treatment, history of appetite suppressant use, and history of neurological illness.

Three-Factor Eating Questionnaire (TFEQ)

Eating behavior was measured using a modified version of the TFEQ[34]. The TFEQ assesses degree of dietary restriction ["How often are you (is your child) dieting in a conscious effort to control your (his/her) weight?"], eating disinhibition ["Do you (does your child) eat sensibly in front of others and splurge alone?"], and hunger level ["How often do you (does your child) feel hungry?"]. Only the 13 initial items on this questionnaire were used. Individuals rated their behavior on a 4-point scale (with lower ratings indicating lower dietary restriction, eating disinhibition, and hunger levels). For individuals with PWS, parents/guardians completed the TFEQ for their child. OB and HWC groups completed a self-report version.

fMRI acquisition

Scanning was performed on a 3 Tesla Siemens Allegra or Trio scanner (Siemens, Erlangen, Germany). Participants' heads were immobilized with cushions. Most subjects (n = 38) were scanned at KUMC on an Allegra scanner using a quadrature headcoil with the five remaining subjects (all PWS) scanned on a Trio scanner using an 8-channel headcoil at URMC. One anatomical and two functional sequences were run in each scanning session

(i.e., pre-meal and post-meal). T1-weighted anatomical images were acquired using 3D MP-RAGE sequences: KUMC - coronal, repetition time/echo time (TR/TE) = 23/4 ms, flip angle = 8°, field of view (FOV) = 256 mm, matrix = 256×192, slice thickness = 1 mm; URMC - sagittal, TR/TE = 20/4 ms, flip angle = 15°, FOV = 256 mm, matrix = 256 × 256, slice thickness = 1 mm. Similar parameters were used at each site for fMRI studies. Single shot gradient echo planar imaging (EPI) fMRI scans were acquired at each site: 43 contiguous coronal slices, TR/TE = 3000/40 ms, flip angle = 90°, FOV = 192 mm, matrix = 64 × 64, slice thickness = 3 mm, in-plane resolution = 3 × 3 mm, 130 data points; at URMC, TE = 36 ms was used. A shorter TE (36 vs. 40 ms) in fMRI scans provides ~7% higher signal-to-noise ratio (SNR) based on the typical T2* in cortical gray matter[35], but ~10% lower task-induced BOLD signal change. Since the fMRI contrast-to-noise ratio (CNR) is proportional to the product of SNR and BOLD signal changes, we estimated ~3% CNR at TE = 36 ms. Therefore, it was expected that the overall effect of the TE difference was not significant and within the range of the experimental variations. Moreover, given the rarity of PWS and the need for larger samples, the compromise of slightly different acquisitions was justified.

Experimental paradigm

Participants viewed pictures of food, animals, and Gaussian-blurred low-level baseline control images during two scanning sessions; one after fasting for four hours (pre-meal; either prior to breakfast at 8:00 am or prior to lunch at 12:00 pm) and one within 15 minutes after eating a small uniform meal (post-meal: either following breakfast at 8:30 am or following lunch at 12:30 pm, respectively). The meal was standardized for total number of calories (kcal = 500), and macro-/micronutrient content. The order of sessions was counterbalanced across subjects.

Activation paradigm

Visual stimuli of two categories (food and blurred baseline control images) were obtained from LaBar and colleagues[36]. Though previous studies have used tools as non-food comparison stimuli[36], due to the mental and chronological age of some of the participants in this study, images of animals were used to keep participants attentive to the task and to control for general familiarity. All images for the animal (non-food) category were obtained from professional photographic sources and matched to food and blurred control images on brightness, resolution, and size. Each image was presented one time only to each subject during scanning.

Visual stimuli were projected through 3D limited-view goggles (Resonance Technology, Inc., Northridge, California) controlled by stimuli-generating software (NeuroSTIM, Neuroscan, El Paso, TX). Each of the two 6.5 minute functional scans involved three repetitions of each 30-second block for stimulus condition type (i.e., food, non-food), alternated with 30-second blocks of blurred images (stimulus presentation time = 2.5 seconds, interstimulus interval (ISI) = 0.5 seconds, 13 blocks/run, 10 images/block). The order of category presentation was counterbalanced across subjects.

Participants were instructed to remember images for a memory test following the scanning session. To confirm they were attending to the stimuli, participants completed a recognition

memory test outside the scanner, immediately following each scanning session. From food and non-food stimuli, 50% of the images were chosen for recall and interspersed with novel distracter images from the same category. Participants were instructed to press one key if they had seen the image in the scanner (old) and another if they had not seen the image (new). Recognition memory task data for 1 PWS subject were excluded due to technical errors.

fMRI data analysis

fMRI data were preprocessed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, 2008) and custom routines in MATLAB (Mathworks, Inc., 2000). Processing commenced with realignment and correction for bulk-head motion. Images for each subject were spatially normalized using nonlinear volume-based spatial normalization techniques and registered to the Montreal Neurological Institute (MNI) standard brain template. Images were then spatially-smoothed with a Gaussian filter (6mm at FWHM). Finally, well-established artifact detection tools (http://web.mit.edu.ezp-prod1.hul.harvard.edu/swg/software.htm) were used to identify and exclude outliers in the global mean image time series and movement parameters. Outliers were defined as: >3.8mm translational movement, >.05 radians rotational movement, or 1.40 standard deviations away from the global mean. Of the original participants/group (n=15/group), two subjects (1 PWS, 1 OB) were excluded due to excessive movement. In addition, evidence of diminished attention due to excessive sleepiness resulted in discarding that run (PWS: 5 out of 56 runs; OB: 2 of 56; HWC: 2 of 58), derived from consensus between authors (L.H. and C.S.) on a combination of self-report of sleeping, review of memory data indicating performance was less than chance, and visual inspection of occipital lobe activation revealing null results to blurred baseline images (indicating that the eyes were likely closed).

Following preprocessing, statistical analysis was performed at the single-subject level using SPM8. SPM8 treats each voxel's BOLD time series according to a general linear model. Each epoch of trials was modeled using a boxcar function convolved with a canonical hemodynamic response function. Specific comparisons of interest (food versus non-food, separately for pre-meal and post-meal) were tested using linear contrasts, and SPM maps were created based on these contrasts. These contrast values (estimates of the mean signal change at each voxel) were used in statistical analyses.

Voxel-wise analysis

Results from the individual subject level were submitted to a second analysis in which subjects were treated as a random effect. Independent sample t-tests were used to compare the size of a particular effect between groups (PWS vs. OB; PWS vs. HWC; OB vs. HWC). Given our hypotheses about specific brain regions, we used an approach in SPM8 which limits voxel-wise analyses to voxels within our a priori regions of interest (ROIs). Anatomically-defined ROIs included the hypothalamus, NAc, amygdala, hippocampus, OFC, and mPFC. Given lack of clear DLPFC cytoarchitectural borders and also the extensive volume of the DLPFC, the DLPFC ROI was defined in a two-step process by combining anatomic and functional approaches. First, we created a mask consisting of Brodmann Areas 10 and 46 (based on the Wake Forest University (WFU) PickAtlas[37]

toolbox) and, using small volume correction, determined the maximum voxel of activation for the food vs. non-food contrast in the HWC group (separately for pre-meal and post-meal sessions). A 10 mm sphere was created around each of these maximum voxel coordinates. This spherical DLPFC ROI was then used for between-group contrasts. Anatomic borders of all remaining hypothesized regions were defined using an in-house manually segmented MNI-152 brain (with the exception of the DLPFC, which was defined as described above). These borders were implemented as overlays on the SPM8 canonical brain using the WFU PickAtlas toolbox. Small volume correction was used to identify clusters which were significant at p<0.05 (uncorrected) and met a cluster-size extent threshold (2 voxels in the hypothalamus and NAc, given their small volumes; 4 voxels for all other ROIs). From these identified clusters, results are reported here for clusters significant at p<0.05 (uncorrected) and p<0.2 [corrected for multiple comparisons within the search volume using family-wise error (FWE) correction] and are considered significant (bolded in the tables) if they reached a voxel-level significance of p<0.05, FWE-corrected.

Anatomical ROI analysis

After identifying clusters within ROIs which were significant at the voxel-level, FWE-corrected, using the methods described above, anatomic overlays were used on the statistical maps of each individual to acquire signal change values across specific ROIs. Values indicated the degree of change in MR signal detected between the food and non-food and are expressed in terms of percent signal change (PSC). Average PSC values (beta weights averaged across all voxels within an anatomical region) were obtained using the REX toolbox for SPM8[38]. Given the particular emphasis on direct PWS vs. OB comparisons in this study, PSC values were used to calculate effect sizes (ES) in order to quantify the differences between PWS and OB groups. The formula for calculating ESs was: ES = [PWS group mean (food – non-food PSC) – OB group mean (food – non-food PSC)]/standard deviation of PSC value of the whole sample.

RESULTS

Behavioral Data

Group comparisons on TFEQ scores tested whether groups differed in problematic eating behavior. Mean TFEQ scores for PWS (2.98 ± 0.41) were significantly higher than OB (2.45 ± 0.29; t = 3.95/p<0.01) and HWC (2.22 ± 0.22; t = 6.38/p<0.01). The OB group had significantly higher mean TFEQ scores than HWC (t = 2.39/p<0.05), suggesting a significant increase in hunger level, disinhibition, and dietary restraint behaviors in the comparison between HWC, OB, and PWS groups (though some caution should be applied since parents/guardians completed the TFEQ for PWS participants).

Performance on the recognition memory test was above chance for all groups (p values <0.01), confirming that subjects were properly attending to visual stimuli during the scanning session. OB and HWC performed significantly better than PWS on recall of both food and non-food stimuli (p values <0.01), likely related to impaired cognitive functioning in PWS[16].

fMRI Data

The main contrasts of interest for this study focused on comparisons of PWS and OB in activations of hypothesized ROIs in response to food vs. non-food stimuli before and after eating. During pre-meal, PWS exhibited significantly greater activations to food stimuli than OB in the NAc and amygdala, uncorrected for multiple comparisons (Table 1). In contrast to PWS, OB showed greater activations in response to food versus non-food stimuli pre-meal in the hypothalamus and hippocampus. Effect sizes for group differences ranged from 0.41 (hypothalamus) to 0.66 (NAc; Table 1).

Comparison of PWS and OB post-meal indicated greater activations in PWS in the hypothalamus, amygdala, and hippocampus (Table 1; Figure 1). Examination of the average percent signal change in each group indicates that greater activity in the amygdala in the PWS group resulted from a marked failure to decrease activity in the PWS group in this region (see Figure 1). Conversely, OB exhibited greater activations post-meal in DLPFC [Brodmann Area (BA) 46] and OFC (BA 11; Figure 1). Group differences in DLPFC were significant when FWE-corrected for multiple comparisons. Effect sizes for group differences ranged from 0.38 (hypothalamus) to 0.95 (DLPFC). To characterize the nature of DLPFC hypoactivation in the PWS group, we examined correlations between DLPFC percent signal change and behavioral characteristics. Although none of these correlations reached significance, the strongest relationship was found between DLPFC activity and TFEQ scores (approaching a trend level; r=0.44; p=0.11). DLPFC activity was unrelated to general IQ (r=0.38, n.s.) and post-meal memory for food items (r=−0.26, n.s.).

In comparisons of OB with HWC, OB exhibited greater activations in response to food versus non-food stimuli in the hypothalamus, amygdala, mPFC, and OFC during the pre-meal condition, and post-meal in the hypothalamus and DLPFC (Table 2). Conversely, HWC displayed greater activation than OB post-meal in OFC.

Finally, PWS exhibited persistent hyperactivation compared to HWC in the hypothalamus, amygdala, and hippocampus pre-meal and post-meal, and in mPFC pre-meal (Table 3). There were no regions in which HWC displayed greater activation than PWS pre-meal or post-meal. Although not the main emphasis of this study, given established sex differences in obesity, we repeated the above analyses of group differences separately in females and males. Results from these analyses, though limited by small sample sizes, were qualitatively similar to the findings in the mixed-sex analyses.

DISCUSSION

Converging evidence on neural substrates of abnormal food intake and obesity has implicated somewhat overlapping but distinct neural circuits related to hunger/satiety, reward, and self-control. Our results extend these findings and suggest unique patterns of brain activation in these regions in two groups of individuals with different types of obesity: one group with a genetic syndrome and phenotype that includes extreme overeating (PWS), the other with (idiopathic) OB. Specifically, we report hyperactivations in response to visual food stimuli in individuals with PWS compared to BMI-matched OB subjects in subcortical regions (hypothalamus, hippocampus) depending on appetitive state. Altered function in the

amygdala in PWS vs. OB was unaffected by state, with hyperactivation both before and after meal consumption. In particular, post-meal abnormalities in the amygdala resulted from failure to demonstrate *decreased* activation, which could be one factor affecting disruption of satiety mechanisms in PWS. More strikingly, individuals with PWS displayed significant hypoactivity in prefrontal cortical regions (posterior/lateral OFC, DLPFC) post-meal. The brain activation patterns distinguishing these groups map well onto the differences observed between PWS and OB in eating behavior (extreme hyperphagia versus moderate overeating), energy expenditure (very low versus moderately low), and appetite-regulatory peptide levels (hyperghrelinemia versus low ghrelin), and thus support the conceptualization of PWS as a model of extreme obesity.

Pre-meal subcortical hyperactivation in response to visual food stimuli and to glucose ingestion has been documented previously in OB[1] and PWS[28,39] in comparison to healthy-weight controls, and post-meal in OB[4] and in PWS[30,39,40] [a]. These regions (hypothalamus, amygdala, hippocampus), which are densely populated with ghrelin receptors[41–46], are involved in basic hunger and satiety signaling[45], reward and approach behaviors related to food[47–50], and emotion-modulated memory processes involved with food[51], respectively. Our results replicate and extend these findings by demonstrating that subcortical reward circuitry hyperactivation in response to food stimuli is a hallmark of obesity and disorders of obesity (i.e., PWS), and is independent of appetitive state.

The most noteworthy finding in this study relates to post-meal differences between PWS and simple OB in putative cortical inhibitory regions (DLPFC, OFC) with significant effect sizes in the range of 0.75 to 1.0 full standard deviation from the mean. We note the paradigm used in the current study did not directly manipulate inhibitory demands or measure inhibition outside of the scanner. However, the DLPFC is well-established as a critical inhibitory region, associated with suppression of motor responses[52] and higher-level cognitive processes such as self-control in goal-directed behavior and decision-making[53,54], including issues involving food intake. Evidence for this role includes greater DLPFC activation in response to: meal consumption in successful dieters compared with non-dieting obese individuals[55], food pictures[15] or satiety[56] for obese children[15] and adult males[56] in comparison to healthy-weight counterparts, self-control trials for high-self-controllers versus non-self-controllers[13], inhibitory control in a food go/no-go task in lean compared with overweight adolescents[57], and tasting palatable food[14] for individuals with high dietary restraint scores. Thus, based on previous findings of activation in this region during tasks requiring inhibition[58–60], one possible interpretation of the current DLPFC hypoactivation in PWS is that it reflects deficits in inhibitory control. Hypoactivation in similar frontal regions in a task-switching paradigm has also been reported in PWS, providing additional evidence of prefrontal circuitry deficits related to executive functioning[61]. This hypothesis should be more directly tested in future studies. Further, genetic variability related to subtle differences in behavioral profiles in PWS[62] was significantly associated with differential activation of DLPFC post-meal[39], suggesting a genetic basis for abnormal activation in this cortical

---

[a] However, recent work suggests a more complex relationship, citing an association between weight *gain* and *reduced* activity in response to imagined ingestion[7] of palatable foods in reward regions such as the striatum, which might be related to allelic variation in DRD2 and DRD4 dopamine transporter genes.

region associated with inhibitory control in obesity. Failure of DLPFC recruitment in PWS may result from abnormalities in $GABA_A$ receptors in the frontal cortex[63], likely related to deletion of GABA receptor subunit genes from the ~6-Mb PWS region of chromosome 15[18]. Our work to further define the brain phenotype in PWS will help direct molecular genetics studies to identify additional genes and polymorphisms on chromosome 15 associated with specific brain abnormalities. This may, in turn, contribute to understanding genes associated with brain circuitry implicated in OB.

Our findings suggest that hyperactivation of the DLPFC post-meal might be associated with either the greater ability or heightened need to inhibit food-related behaviors and intake, reflecting the necessity of additional top-down inhibition in the presence of high-reward food stimuli. In light of these results, we suggest that hyperactivation of DLPFC in OB versus PWS post-meal might reflect successful recruitment (i.e., ability to activate the DLPFC in a situation requiring inhibition) of this important inhibitory self-control region in individuals who overeat moderately, and unsuccessful activation of DLPFC in PWS, contributing to hyperphagia and excessive overeating.

PWS is associated with intellectual disability, including deficits in abstract reasoning and executive functioning, domains which are also governed substantially by DLPFC. Thus, to parse out what might be driving hypoactivation in this region, we explored the relationships between DLPFC activation and specific executive functioning and general cognitive ability. PWS hypoactivation in DLPFC was unrelated to memory for food items and moderately associated with general IQ, which is not surprising, given that the DLPFC is involved in multiple executive processes. However, we argue that global intellectual deficits were not driving the DLPFC effects of inhibition around food, given the strongest correlation (although not significant) was between DLPFC activation and TFEQ, suggesting the most substantial link was between deficits in this area and *food-related* behaviors. Based on these findings, inability to recruit the DLPFC in response to food cues after eating may represent what distinguishes PWS from OB.

In addition to hypoactivation of DLPFC in the current study, PWS exhibited lower activation post-meal compared with OB in left posterior-lateral OFC, a region associated with evaluation of simple stimuli (such as food images) in the context of punishment leading to behavior changes[64]. OFC hypoactivation in response to food stimuli post-meal has previously been associated with higher BMI[10,11], including in individuals with fewer striatal dopamine receptors[7] [b]. Further, dysfunction in the amygdala's modulation of OFC was reported in OB[65], and OFC volume was specifically decreased in PWS compared with healthy controls[66].

We hypothesize that concurrent dysfunction in OFC and DLPFC in PWS might significantly impair the ability to effectively inhibit food intake during states of low appetite (post-meal, when consumption would be primarily for hedonic purposes rather than energy balance

---

[b]We note that opposite trends (OFC *hyper*activation; *positive* correlation between BMI and OFC activation to high-calorie food pictures) have also been reported in individuals with obesity[1,2], although in these studies, subjects were scanned either pre-meal (while hungry) or "neither hungry nor just satiated", in contrast to our finding of OFC hypoactivation *post-meal*, making it somewhat difficult to draw clear comparisons.

maintenance). We argue that subcortical *hyper*activation combined with cortical *hypo*activation contributes importantly to the phenotype of excessive hunger, uncontrollable food seeking behavior, and hyperphagia in PWS as distinct from OB, in which more intact functioning in these regions results in a less extreme behavioral profile.

In the current investigation, we replicated previous findings from fMRI studies comparing PWS versus HWC[28,29,39] and OB versus HWC[1,3,10], with results suggesting hyperactivation in subcortical and cortical food motivation regions in the OB and PWS groups both pre- and post-meal. To date, our study includes the largest sample in an fMRI study of BMI-matched PWS and OB groups; thus inconsistencies between previous studies may be resolved given increased statistical power of our tests. In addition to these strengths, we note the following limitations of this study. Rather than match meal sizes to each subject's corresponding caloric homeostatic needs, we developed our meal size according to the restricted diets that are characteristic for PWS, which may have influenced the level to which each individual felt satiated and affected patterns of activation. However, given that our OB and PWS groups were matched on BMI, this was unlikely to be a confounder. We did not assess hunger level before and after the meal, which might have assisted in validating the satiating effect of the meal across groups. Future studies should incorporate hunger ratings that can be used with individuals with and without intellectual disabilities. In our sample, the PWS group likely had a significantly lower mean IQ than the other groups. However, behavioral results indicated greater-than-chance accuracy on the recognition memory test in all groups, suggesting that all subjects were able to perform the task. The original design of this study did not include neurobehavioral testing in OB and HWC, so we were unable to explore relationships between brain activity and other cognitive/behavioral functioning which may contribute to understanding differences between PWS and OB. In our PWS sample, data acquired under slightly different TEs were included reflecting inter-instrumental differences. The minimal effect (~3%) on the contrast-to-noise ratio was less than the expected experimental variation. Indeed, sub-analysis of the KUMC data yielded similar findings (data not shown), indicating that site and TE differences did not affect our results. Finally, there are significant sex differences in obesity[67], and several of our ROIs are sexually dimorphic[68]. Given that the majority of our participants were female, especially in the PWS group, it was not possible to conduct an analysis of sex differences. However, analysis of females and males found qualitatively similar results.

In summary, this study demonstrates dysfunction in dual circuits which are involved in the regulation of food reward and in putative decision-making processes regarding food intake in individuals with PWS, a putative model of extreme obesity compared with OB. In a post-meal state, PWS compared to OB demonstrated hyperactivations in the subcortical regions associated with hunger and food motivation and hypoactivations in cortical regions involved in self-control during food-related decision-making. These findings provide evidence of distinct neural patterns that correspond with group differences in eating behavior (degree of overeating) despite similar BMI levels, and suggest neural pathways that can be targeted in future studies of the treatment of obesity and related conditions.

ACKNOWLEDGEMENTS

REFERENCES

1. Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage. 2008; 41:636–647. [PubMed: 18413289]

2. Rothemund Y, Preuschhof C, Bohner G, Bauknecht HC, Klingebiel R, Flor H, et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage. 2007; 37:410–421. [PubMed: 17566768]

3. Martin LE, Holsen LM, Chambers RJ, Bruce AS, Brooks WM, Zarcone JR, et al. Neural mechanisms associated with food motivation in obese and healthy weight adults. Obesity. 2010; 18:254–260. [PubMed: 19629052]

4. Matsuda M, Liu Y, Mahankali S, Pu Y, Mahankali A, Wang J, et al. Altered hypothalamic function in response to glucose ingestion in obese humans. Diabetes. 1999; 48:1801–1806. [PubMed: 10480611]

5. Stice E, Yokum S, Burger KS, Epstein LH, Small DM. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. Journal of Neuroscience. 2011; 31:4360–4366. [PubMed: 21430137]

6. Stice E, Yokum S, Blum K, Bohon C. Weight gain is associated with reduced striatal response to palatable food. Journal of Neuroscience. 2010; 30:13105–13109. [PubMed: 20881128]

7. Stice E, Yokum S, Bohon C, Marti N, Smolen A. Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. Neuroimage. 2010; 50:1618–1625. [PubMed: 20116437]

8. Alonso-Alonso M, Pascual-Leone A. The right brain hypothesis for obesity. JAMA. 2007; 297:1819–1822. [PubMed: 17456824]

9. Breslin FJ, Lepping RJ, Hay TM, Martin LE, Bruce AS, Lynch AM, et al. Differential encoding of food pictures in successful and unsuccessful dieters. Obesity. 2010; 18(Suppl 2):S77. (abstract 130-P).

10. Bruce AS, Holsen LM, Chambers RJ, Martin LE, Brooks WM, Zarcone JR, et al. Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. International Journal of Obesity. 2010; 34:1494–1500. [PubMed: 20440296]

11. Killgore WD, Yurgelun-Todd DA. Body mass predicts orbitofrontal activity during visual presentations of high-calorie foods. Neuroreport. 2005; 16:859–863. [PubMed: 15891585]

12. Sescousse G, Redoute J, Dreher JC. The architecture of reward value coding in the human orbitofrontal cortex. Journal of Neuroscience. 2010; 30:13095–13104. [PubMed: 20881127]

13. Hare TA, Camerer CF, Rangel A. Self-control in decision-making involves modulation of the vmPFC valuation system. Science. 2009; 324:646–648. [PubMed: 19407204]

14. Burger KS, Stice E. Relation of dietary restraint scores to activation of reward-related brain regions in response to food intake, anticipated intake, and food pictures. Neuroimage. 2011; 55:233–239. [PubMed: 21147234]

15. Davids S, Lauffer H, Thoms K, Jagdhuhn M, Hirschfeld H, Domin M, et al. Increased dorsolateral prefrontal cortex activation in obese children during observation of food stimuli. International Journal of Obesity. 2010; 34:94–104. [PubMed: 19806158]

16. Butler MG. Prader-Willi syndrome: current understanding of cause and diagnosis. American Journal of Medical Genetics. 1990; 35:319–332. [PubMed: 2309779]

17. Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H. Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. Journal of Medical Genetics. 2001; 38:792–798. [PubMed: 11732491]

18. Bittel DC, Butler MG. Prader-Willi syndrome: clinical genetics, cytogenetics and molecular biology. Expert Rev Mol Med. 2005; 7:1–20. [PubMed: 16038620]

19. Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, et al. Gastric rupture and necrosis in Prader-Willi syndrome. Journal of Pediatric Gastroenterology and Nutrition. 2007; 45:272–274. [PubMed: 17667731]

20. Kennedy L, Bittel DC, Kibiryeva N, Kalra SP, Torto R, Butler MG. Circulating adiponectin levels, body composition and obesity-related variables in Prader-Willi syndrome: comparison with obese subjects. International Journal of Obesity. 2006; 30:382–387. [PubMed: 16231029]

21. Theodoro MF, Talebizadeh Z, Butler MG. Body composition and fatness patterns in Prader-Willi syndrome: comparison with simple obesity. Obesity. 2006; 14:1685–1690. [PubMed: 17062796]

22. Butler MG, Theodoro MF, Bittel DC, Donnelly JE. Energy expenditure and physical activity in Prader-Willi syndrome: comparison with obese subjects. Am J Med Genet A. 2007; 143:449–459. [PubMed: 17103434]

23. Proto C, Romualdi D, Cento RM, Romano C, Campagna G, Lanzone A. Free and total leptin serum levels and soluble leptin receptors levels in two models of genetic obesity: the Prader-Willi and the Down syndromes. Metabolism: Clinical and Experimental. 2007; 56:1076–1080. [PubMed: 17618952]

24. Haqq AM, Farooqi IS, O'Rahilly S, Stadler DD, Rosenfeld RG, Pratt KL, et al. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader-Willi syndrome. Journal of Clinical Endocrinology and Metabolism. 2003; 88:174–178. [PubMed: 12519848]

25. Zipf WB, Berntson GG. Characteristics of abnormal food-intake patterns in children with Prader-Willi syndrome and study of effects of naloxone. American Journal of Clinical Nutrition. 1987; 46:277–281. [PubMed: 3618531]

26. Lindgren AC, Barkeling B, Hagg A, Ritzen EM, Marcus C, Rossner S. Eating behavior in Prader-Willi syndrome, normal weight, and obese control groups. Journal of Pediatrics. 2000; 137:50–55. [PubMed: 10891821]

27. Dykens EM, Maxwell MA, Pantino E, Kossler R, Roof E. Assessment of hyperphagia in Prader-Willi syndrome. Obesity. 2007; 15:1816–1826. [PubMed: 17636101]

28. Dimitropoulos A, Schultz RT. Food-related neural circuitry in Prader-Willi syndrome: response to high- versus low-calorie foods. Journal of Autism and Developmental Disorders. 2008; 38:1642–1653. [PubMed: 18311513]

29. Holsen LM, Zarcone JR, Brooks WM, Butler MG, Thompson TI, Ahluwalia JS, et al. Neural mechanisms underlying hyperphagia in Prader-Willi syndrome. Obesity. 2006; 14:1028–1037. [PubMed: 16861608]

30. Shapira NA, Lessig MC, He AG, James GA, Driscoll DJ, Liu Y. Satiety dysfunction in Prader-Willi syndrome demonstrated by fMRI. Journal of Neurology, Neurosurgery and Psychiatry. 2005; 76:260–262.

31. Miller JL, James GA, Goldstone AP, Couch JA, He G, Driscoll DJ, et al. Enhanced activation of reward mediating prefrontal regions in response to food stimuli in Prader-Willi syndrome. Journal of Neurology, Neurosurgery and Psychiatry. 2007; 78:615–619.

32. Hinton EC, Holland AJ, Gellatly MS, Soni S, Patterson M, Ghatei MA, et al. Neural representations of hunger and satiety in Prader-Willi syndrome. International Journal of Obesity. 2006; 30:313–321. [PubMed: 16276365]

33. Butler MG, Bittel DC, Kibiryeva N, Talebizadeh Z, Thompson T. Behavioral differences among subjects with Prader-Willi syndrome and type I or type II deletion and maternal disomy. Pediatrics. 2004; 113:565–573. [PubMed: 14993551]

34. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. Journal of Psychosomatic Research. 1985; 29:71–83. [PubMed: 3981480]

35. Gelman N, Gorell JM, Barker PB, Savage RM, Spickler EM, Windham JP, et al. MR imaging of human brain at 3.0 T: preliminary report on transverse relaxation rates and relation to estimated iron content. Radiology. 1999; 210:759–767. [PubMed: 10207479]

36. LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behavioral Neuroscience. 2001; 115:493–500. [PubMed: 11345973]

37. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage. 2003; 19:1233–1239. [PubMed: 12880848]

38. Whitfield-Gabrieli, S. Region of Interest Extraction (REX) Toolbox. Boston, MA: 2009.

39. Holsen LM, Zarcone JR, Chambers R, Butler MG, Bittel DC, Brooks WM, et al. Genetic subtype differences in neural circuitry of food motivation in Prader-Willi syndrome. International Journal of Obesity. 2009; 33:273–283. [PubMed: 19048015]

40. Holsen LM, Zarcone JR, Thompson TI, Brooks WM, Anderson MF, Ahluwalia JS, et al. Neural mechanisms underlying food motivation in children and adolescents. Neuroimage. 2005; 27:669–676. [PubMed: 15993629]

41. Guan XM, Yu H, Palyha OC, McKee KK, Feighner SD, Sirinathsinghji DJ, et al. Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. Brain Research Molecular Brain Research. 1997; 48:23–29. [PubMed: 9379845]

42. Hosoda H, Kojima M, Kangawa K. Biological, physiological, and pharmacological aspects of ghrelin. J Pharmacol Sci. 2006; 100:398–410. [PubMed: 16612045]

43. Howard AD, Feighner SD, Cully DF, Arena JP, Liberator PA, Rosenblum CI, et al. A receptor in pituitary and hypothalamus that functions in growth hormone release. Science. 1996; 273:974–977. [PubMed: 8688086]

44. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, et al. A role for ghrelin in the central regulation of feeding. Nature. 2001; 409:194–198. [PubMed: 11196643]

45. Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. Neuron. 2002; 36:199–211. [PubMed: 12383777]

46. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000; 404:661–671. [PubMed: 10766253]

47. Holland PC, Gallagher M. Amygdala circuitry in attentional and representational processes. Trends Cogn Sci. 1999; 3:65–73. [PubMed: 10234229]

48. Petrovich GD, Setlow B, Holland PC, Gallagher M. Amygdalo-hypothalamic circuit allows learned cues to override satiety and promote eating. Journal of Neuroscience. 2002; 22:8748–8753. [PubMed: 12351750]

49. Schoenbaum G, Chiba AA, Gallagher M. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nature Neuroscience. 1998; 1:155–159. [PubMed: 10195132]

50. Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. Brain Research Brain Research Reviews. 2003; 41:88–123. [PubMed: 12505650]

51. Tracy AL, Jarrard LE, Davidson TL. The hippocampus and motivation revisited: appetite and activity. Behavioural Brain Research. 2001; 127:13–23. [PubMed: 11718882]

52. Liddle PF, Kiehl KA, Smith AM. Event-related fMRI study of response inhibition. Human Brain Mapping. 2001; 12:100–109. [PubMed: 11169874]

53. Miller EK. The prefrontal cortex and cognitive control. Nat Rev Neurosci. 2000; 1:59–65. [PubMed: 11252769]

54. Tanji J, Hoshi E. Role of the lateral prefrontal cortex in executive behavioral control. Physiological Reviews. 2008; 88:37–57. [PubMed: 18195082]

55. DelParigi A, Chen K, Salbe AD, Hill JO, Wing RR, Reiman EM, et al. Successful dieters have increased neural activity in cortical areas involved in the control of behavior. International Journal of Obesity. 2007; 31:440–448. [PubMed: 16819526]

56. Gautier JF, Chen K, Salbe AD, Bandy D, Pratley RE, Heiman M, et al. Differential brain responses to satiation in obese and lean men. Diabetes. 2000; 49:838–846. [PubMed: 10905495]

57. Batterink L, Yokum S, Stice E. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. Neuroimage. 2010; 52:1696–1703. [PubMed: 20510377]

58. Bellgrove MA, Hester R, Garavan H. The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. Neuropsychologia. 2004; 42:1910–1916. [PubMed: 15381021]

59. Chikazoe J, Jimura K, Asari T, Yamashita K, Morimoto H, Hirose S, et al. Functional dissociation in right inferior frontal cortex during performance of go/no-go task. Cerebral Cortex. 2009; 19:146–152. [PubMed: 18445602]

60. Evers EA, van der Veen FM, van Deursen JA, Schmitt JA, Deutz NE, Jolles J. The effect of acute tryptophan depletion on the BOLD response during performance monitoring and response inhibition in healthy male volunteers. Psychopharmacology. 2006; 187:200–208. [PubMed: 16710715]

61. Woodcock KA, Humphreys GW, Oliver C, Hansen PC. Neural correlates of task switching in paternal 15q11-q13 deletion Prader-Willi syndrome. Brain Research. 2010; 1363:128–142. [PubMed: 20920489]

62. Webb T, Whittington J, Clarke D, Boer H, Butler J, Holland A. A study of the influence of different genotypes on the physical and behavioral phenotypes of children and adults ascertained clinically as having PWS. Clinical Genetics. 2002; 62:273–281. [PubMed: 12372053]

63. Lucignani G, Panzacchi A, Bosio L, Moresco RM, Ravasi L, Coppa I, et al. GABA A receptor abnormalities in Prader-Willi syndrome assessed with positron emission tomography and [11C]flumazenil. Neuroimage. 2004; 22:22–28. [PubMed: 15109994]

64. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci. 2005; 6:691–702. [PubMed: 16136173]

65. Stoeckel LE, Kim J, Weller RE, Cox JE, Cook EW 3rd, Horwitz B. Effective connectivity of a reward network in obese women. Brain Research Bulletin. 2009; 79:388–395. [PubMed: 19467298]

66. Ogura K, Fujii T, Abe N, Hosokai Y, Shinohara M, Takahashi S, et al. Small gray matter volume in orbitofrontal cortex in Prader-Willi syndrome: A voxel-based MRI study. Human Brain Mapping. 2010

67. Wang Y, Beydoun MA. The obesity epidemic in the United States--gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. Epidemiologic Reviews. 2007; 29:6–28. [PubMed: 17510091]

68. Goldstein JM, Seidman LJ, Horton NJ, Makris N, Kennedy DN, Caviness VS Jr, et al. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cerebral Cortex. 2001; 11:490–497. [PubMed: 11375910]
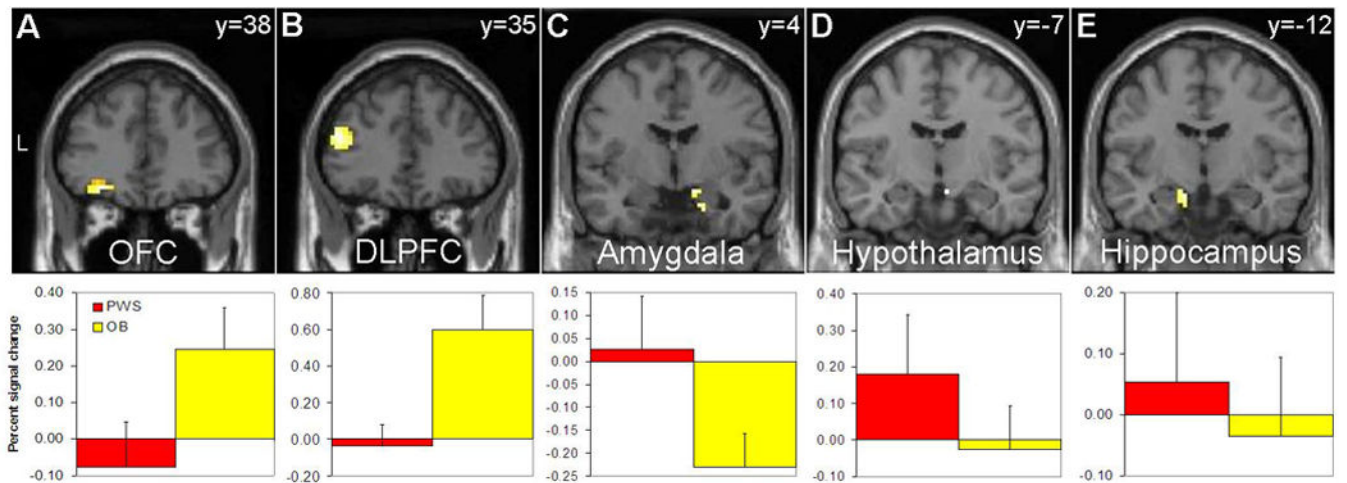
Figure 1.

Comparison of PWS and OB groups for the food > non-food contrast in the **Post-Meal** condition. Regions demonstrating greater activation in the OB group compared to the PWS group (OB > PWS) include the left OFC (A) and left DLPFC (B). Greater activation in the PWS vs. OB group was seen in the right amygdala (C), right hypothalamus (D), and left hippocampus (E). Activation overlaid on the SPM8 single-subject T1 template in the coronal view. Bar graphs depicting average percent signal change in each group for corresponding ROIs are displayed below each ROI image. Error bars reflect the standard error of the mean.

Table 1

Regions reaching significance for the between-group analysis (PWS vs. OB) contrast between food and non-food categories.

Condition	Contrast	Region of Interest	Hemisphere	Voxels	x	y	z[1]	Z-score	Uncorrected p-value[2]	Voxel-level $P_{FWE-corr}$[3]	Effect size of group difference[4]
Pre-meal	PWS > OB										
		Nucleus accumbens	R	2	5	14	0	2.41	0.008	0.081	0.66
		Amygdala	R	11	23	−9	−5	2.21	0.014	0.191	0.45
	OB > PWS										
		Hypothalamus	L	2	−6	−3	−11	2.15	0.016	0.197	0.41
		Hippocampus	L	4	−26	−26	−5	2.68	0.006	0.154	0.47
Post-meal	PWS > OB										
		Hypothalamus	R	5	5	−9	−11	2.71	0.003	0.063	0.38
		Amygdala	R	14	14	0	−11	2.59	0.005	0.089	0.68
		Hippocampus	L	8	−12	−12	−13	2.72	0.003	0.093	0.68
	OB > PWS										
		DLPFC	L	50	−44	34	19	2.75	0.003	**0.039**	0.95
		OFC	L	53	−27	33	−11	3.35	0.000	0.097	0.72

[1] Coordinates are presented in Talairach space

[2] Voxel-wise Z-score significance level p<0.05 uncorrected for multiple comparisons within a hypothesized ROI; ROIs listed represent regions of significantly activated clusters within the a priori hypothesized ROI

[3] FWE rate (family-wise error rate) used for SVC (small volume correction): Voxel-level significance level (FWE-corrected within the search volume of interest)

[4] ES (Effect sizes) = standard deviations calculated as: differences between food versus non-food percent signal changes in PWS vs. OB; differences are divided by standard deviation of percent signal change value of the whole sample

Table 2

Regions reaching significance for the between-group analysis (OB vs. HWC) contrast between food and non-food categories.

Condition	Contrast	Region of Interest	Hemisphere	Voxels	x	y	z^1	Z-score	Uncorrected p-value[2]	Voxel-level $P_{FWE-corr}$ [3]
Pre-meal	OB > HWC									
		Hypothalamus	L	19	−3	−9	−3	2.89	0.002	**0.048**
			R	19	5	−3	−6	2.76	0.003	0.064
		Amygdala	L	14	−29	−4	−14	2.44	0.007	0.137
		OFC	L	43	−30	6	−17	3.43	0.000	0.092
		mPFC	R	18	2	54	9	3.18	0.001	0.062
	HWC > OB	*none*								
Post-meal	OB > HWC									
		Hypothalamus	R	7	5	−9	−6	2.61	0.004	0.080
		DLPFC	L	30	−44	37	21	2.47	0.007	0.075
	HWC > OB									
		OFC	R	17	23	21	−12	3.14	0.001	0.164

[1] Coordinates are presented in Talairach space

[2] Voxel-wise Z-score significance level p<0.05 uncorrected for multiple comparisons within a hypothesized ROI; ROIs listed represent regions of significantly activated clusters within the a priori hypothesized ROI

[3] FWE rate (family-wise error rate) used for SVC (small volume correction): Voxel-level significance level (FWE-corrected within the search volume of interest)

Table 3

Regions reaching significance for the between-group analysis (PWS vs. HWC) contrast between food and non-food categories.

Condition	Contrast	Region of Interest	Hemisphere	Voxels	x	y	z^1	Z-score	Uncorrected p-value[2]	Voxel-level $P_{FWE-corr}$ [3]
Pre-meal	PWS > HWC									
		Hypothalamus	L	10	−6	−9	−3	3.41	0.000	**0.011**
		Amygdala	R	47	26	−4	−21	3.38	0.000	**0.026**
			L	34	−20	−9	−13	3.16	0.001	**0.047**
		Hippocampus	L	27	−14	−34	0	3.02	0.001	0.082
		mPFC	L	33	−9	44	−15	2.89	0.002	0.151
	HWC > PWS									
		none								
Post-meal	PWS > HWC									
		Hypothalamus	R	15	2	−9	−8	3.03	0.001	**0.029**
		Amygdala	R	19	14	−9	−13	2.59	0.005	0.088
		Hippocampus	R	43	17	−15	−16	3.56	0.000	**0.031**
	HWC > PWS									
		none								

[1] Coordinates are presented in Talairach space

[2] Voxel-wise Z-score significance level p<0.05 uncorrected for multiple comparisons within a hypothesized ROI; ROIs listed represent regions of significantly activated clusters within the a priori hypothesized ROI

[3] FWE rate (family-wise error rate) used for SVC (small volume correction): Voxel-level significance level (FWE-corrected within the search volume of interest)