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# Neural Mechanisms Underlying Hyperphagia in Prader-Willi Syndrome

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## Abstract

**Objective—**Prader-Willi syndrome (PWS) is a genetic disorder associated with developmental delay, obesity, and obsessive behavior related to food consumption. The most striking symptom of PWS is hyperphagia; as such, PWS may provide important insights into factors leading to overeating and obesity in the general population. We used functional magnetic resonance imaging to study the neural mechanisms underlying responses to visual food stimuli, before and after eating, in individuals with PWS and a healthy weight control (HWC) group.

**Research Methods and Procedures—**Participants were scanned once before (pre-meal) and once after (post-meal) eating a standardized meal. Pictures of food, animals, and blurred control images were presented in a block design format during acquisition of functional magnetic resonance imaging data.

**Results—**Statistical contrasts in the HWC group showed greater activation to food pictures in the pre-meal condition compared with the post-meal condition in the amygdala, orbitofrontal cortex, medial prefrontal cortex (medial PFC), and frontal operculum. In comparison, the PWS group exhibited greater activation to food pictures in the post-meal condition compared with the pre-meal condition in the orbitofrontal cortex, medial PFC, insula, hippocampus, and parahippocampal gyrus. Between-group contrasts in the pre- and post-meal conditions confirmed group differences, with the PWS group showing greater activation than the HWC group after the meal in food motivation networks.

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**Discussion—**Results point to distinct neural mechanisms associated with hyperphagia in PWS. After eating a meal, the PWS group showed hyperfunction in limbic and para-limbic regions that drive eating behavior (e.g., the amygdala) and in regions that suppress food intake (e.g., the medial PFC).

### Keywords

amygdala; Prader-Willi syndrome; functional magnetic resonance imaging; food motivation; genetics

## Introduction

Rates of obesity have risen in the United States to the point of epidemic status (1–3). Obesity is associated with high morbidity and mortality (4), and the direct and indirect health care costs resulting from treatment of obesity are estimated at $117 billion (5). While obesity is a complex problem, one important factor is likely to be differences in brain function (6). However, research into the neural mechanisms contributing to obesity remains in its infancy (6), with no consensus on abnormalities in specific regions.

Prader-Willi syndrome (PWS),[1] a genetic disorder associated with 15q11-q13 deletion or maternal uniparental disomy of chromosome 15, might serve as a unique model of obesity. Phenotypic characteristics of PWS include extreme hyperphagia, obesity, and mild to moderate intellectual disability (7,8). Individuals with PWS consume up to three times the normal caloric intake at a given meal, hoard food, and eat from the garbage (9,10). There are also case reports of stomach rupture arising from extreme overeating (11). Approximately one third of the PWS population maintains >200% of their ideal body weight (12). Identifying neural mechanisms underlying food motivation in PWS, a disorder with known genetic links to hyperphagia, may provide important insights into factors contributing to obesity in the general population.

Relatively few studies have systematically investigated brain structure and function in PWS. Postmortem anatomical and histopathological studies have shown enlarged lateral ventricle volume (13–15), cerebellar dentate nucleus abnormalities (13,16), neuron cell layer disorganization and cell loss (13,16), and frontal cortical atrophy (15,16). Leonard et al. (17) reported abnormal sylvian fissure asymmetry in one half of their PWS sample. Despite its central role in regulating food intake, there seem to be inconsistent findings related to abnormalities in the hypothalamus. For example, individuals with PWS have decreased cerebrospinal fluid (CSF) levels of orexin/hypocretin-1, a hypothalamic neuropeptide that regulates sleep cycles (18). However, Cacciari et al. (19) failed to reveal gross structural abnormalities in the hypothalamus in PWS. Paraventricular hypothalamic oxytocin cells seem to be selectively decreased in PWS (20), although others report elevated CSF levels of oxytocin (21). Finally, compared with controls, individuals with PWS exhibit similar patterns of receptor expression of the orexigenic hormone, ghrelin, in several brain regions (22), despite elevated plasma ghrelin levels in PWS compared with both obese and lean individuals (23).

Functional magnetic resonance imaging (fMRI) provides a non-invasive measure of brain function. A recently published fMRI study of three individuals with PWS showed delayed signal reduction after glucose administration in the hypothalamus, ventromedial prefrontal cortex, and nucleus accumbens, with signal increase in the dorsolateral prefrontal cortex (24). Individuals with PWS had a mean signal reduction latency of 24 minutes after glucose

[1]Nonstandard abbreviations: PWS, Prader-Willi syndrome; CSF, cerebrospinal fluid; fMRI, functional magnetic resonance imaging; OFC, orbitofrontal cortex; PFC, prefrontal cortex; HWC, healthy weight control.

ingestion, compared with a 15-minute mean latency in obese individuals. These findings provide evidence for dysfunction in neural satiety mechanisms in individuals with PWS.

Functional imaging studies in healthy-weight individuals have implicated limbic and paralimbic regions of the brain, including the orbitofrontal cortex (OFC), medial prefrontal cortex (PFC), insula, and amygdala, in processes underlying hunger and food motivation (25–28). These regions have also been implicated in other types of motivated behavior, such as drug craving (29,30). In obese individuals, the PFC seems to exhibit elevated activity during satiation (31), perhaps indicating increased recruitment of the PFC to suppress hyperactive limbic and paralimbic food motivation regions.

This study sought to investigate the neural basis of abnormal food motivation in PWS using fMRI to measure brain responses to visual food stimuli before and after eating a meal. Findings might provide important insights into the neural systems driving hyperphagia in PWS and, ultimately, lead to new research aimed at understanding neural mechanisms underlying obesity in the general population.

## Research Methods and Procedures

### Subjects

Written informed consent and assent were obtained from nine individuals (eight women and one man) with PWS (PWS group) and nine psychiatrically normal, typically developing, healthy-weight control subjects (six women and three men; HWC group). Diagnosis of PWS was confirmed through chromosomal and DNA molecular analysis. Seven PWS subjects were diagnosed with the deletion subtype, whereas two had uniparental disomy. Concomitant psychotropic medications in the PWS group included clonazepam and escitalopram in one subject. Additionally, one PWS participant was being treated for hypothyroidism. Among the PWS participants, three were currently on growth hormone treatment and one additional participant had a previous history of growth hormone treatment; none had a history of appetite suppressant use. Groups were matched on age (HWC group: 14.4 ± 3.0 years, PWS group: 14.7 ± 5.3 years). The HWC group had a significantly higher IQ (HWC group: 117.8 ± 11.6; PWS group: 65.0 ± 13.9; $p < 0.01$, Student's $t$ test) and a significantly lower BMI for age and sex as determined by standardized charts from the United States Centers for Disease Control (HWC group: 18.9 ± 2.6 kg/m$^2$, PWS group: 33.4 ± 16.1 kg/m$^2$; $p < 0.05$, Student's $t$ test). Three individuals in the PWS group and one HWC subject were left-handed. All subjects were without any history of neurological illness. This study was approved by the Human Subjects Committee at the University of Kansas Medical Center.

### fMRI Acquisition

Scanning was performed on a 3-T Siemens Allegra scanner (Siemens, Erlangen, Germany) fitted with a quadrature head coil. Participants' heads were immobilized with head cushions. T1-weighted anatomic images were acquired with a three-dimensional MP-RAGE sequence (repetition time/echo time = 23/4 ms, flip angle = 8°, field of view = 256 mm, matrix = 256 × 192, slice thickness = 1 mm). Single shot gradient echo planar imaging fMRI scans were acquired in 43 contiguous coronal slices [repetition time/echo time = 3000/40 ms, flip angle = 90°, field of view = 192 mm, matrix = 64 × 64, slice thickness = 3 mm (0.5-mm skip), in-plane resolution = 3 × 3 mm, 130 data points]. One anatomical and two functional sequences were run in each scanning session (i.e., pre-meal and post-meal).

### Experimental Paradigm

The experimental paradigm was based closely on LaBar et al. (25). Participants viewed pictures of food, animals, and blurred low-level baseline control images during two scanning sessions:

one after fasting for 4 hours (pre-meal) and one immediately after eating a small uniform meal (post-meal) that was standardized for total number of calories (500 kcal), as well as macro- and micronutrient content. The order of sessions (pre-meal, post-meal) was counterbalanced across subjects so that approximately one half of each group ($n = 5$) started with the pre-meal session and one half ($n = 4$) started with the post-meal session.

### Activation Paradigm

Stimuli of two categories (food and blurred baseline control images) were obtained from LaBar et al. (25). Because of the age of the participants in this study, the comparison stimuli were animals (rather than tools, as used by LaBar et al.), chosen to keep participants attentive to the task and to control for general familiarity. All images for the animal category were obtained from professional stock CD-ROMs and matched to food and blurred control images on brightness, resolution, and size. All images were presented one time only to each subject.

Each functional scan involved three repetitions of each block of each stimulus condition type (i.e., food, animal), alternated between blocks of blurred images. Visual stimuli were projected through three-dimensional limited view goggles (Resonance Technology, Northridge, CA) controlled by the stimuli-generating computer program (NeuroSTIM; Neuroscan, El Paso, TX). Stimulus presentation time was 2.5 seconds, with an interstimulus interval of 0.5 seconds. Within each of the two functional scans, there were 13 blocks of stimulus presentation; within each block, 10 images were presented. The order of category presentation was counterbalanced across subjects.

To ensure that participants were attending to the stimuli being presented, they were instructed to remember images for a memory test after the scanning session. From each of the food and animal groups, ~50% of the images used in the scanning session (30 images) were chosen for recall (old) and interspersed with 15 novel distracter images from the same category (new). Participants completed a recognition memory task outside the scanner, immediately after each scanning session. Participants were instructed to press one key if they had seen the image in the scanner (old) and another key if they had not seen the image (new).

### Behavioral Data Analysis

Because of our small sample size ($n = 18$), we used $A'$ statistics, a non-parametric equivalent of $d'$ (32). Mean $A'$ values were computed for food and non-food items in the pre- and post-meal condition within each group. Wilcoxon signed rank tests (a non-parametric statistic) were used to compare observed performance to chance (i.e., 50% correct).

### fMRI Data Analysis

fMRI data were analyzed using the BrainVoyager 2000 (version 4.9.6) statistical package (Brain Innovation, Maastricht, Netherlands). Preprocessing steps included trilinear three-dimensional motion correction, sinc-interpolated slice scan time correction, three-dimensional spatial smoothing with a 4-mm Gaussian filter, and high-pass filter temporal smoothing. Functional images were realigned to the anatomic images obtained within each session and normalized to the BrainVoyager template image, which conforms to the space defined by the stereotaxic atlas of Talairach and Tournoux (33). Motion in any run of >4 mm along any axis ($x$, $y$, or $z$) resulted in the discard of that run. In addition, behavioral evidence of diminished attention caused by excessive sleepiness resulted in discard of that run. From the HWC group data, 1 run (of 36 total) was discarded; a total of 9 runs (of 36 total) were discarded from the PWS group data.

Activation maps were analyzed using statistical parametric methods (34) as implemented within the BrainVoyager 2000 software. Statistical contrasts were conducted using multiple

regression analysis with the general linear model, allowing for multiple predictors to be built into the model. Regressors representing the experimental conditions of interest were modeled with a hemodynamic response filter and entered into the multiple regression analysis using a fixed-effects model. Contrasts between conditions of interest were assessed with *t* statistics. Statistical parametric maps were overlaid on three-dimensional renderings of an averaged-group brain.

Analysis began with a contrast of blurred control (baseline) vs. food (F) + non-food (NF) within each session and group to assess whether the low-level baseline produced unique areas of significant activation. No significant regions of change were noted. Second, we conducted within-group analyses of response to food vs. non-food images separately within each session (pre- and post-meal). In addition, a within-group interaction analysis was performed to confirm activation to food (vs. baseline) between the pre-meal and post-meal conditions in a priori regions. Finally, a group interaction analysis (PWS vs. HWC) examined response to food (vs. baseline) within each state (pre- and post-meal) to verify group differences in response to food stimuli. Based on a priori regions of interest, voxel values in the amygdala, OFC, medial PFC, insula/frontal operculum, hippocampus, parahippocampal gyrus, and fusiform gyrus were considered significant if the activation survived a statistical threshold of $p < 0.05$ (corrected for multiple comparisons for whole brain) and had a minimum cluster size of three voxels. Other areas were considered significant if they exceeded a threshold of $p < 0.01$ (corrected for whole brain) and had a minimum cluster size of six voxels.

## Results

### Behavioral Data

Individuals in both groups performed significantly better than chance on overall recognition for food and animal images during both sessions. Memory performance scores for both the pre-meal and post-meal sessions were higher than chance in the HWC group (pre-meal: $Z = -2.67$, $p < 0.01$; post-meal: $Z = -2.67$, $p < 0.01$, Wilcoxon signed rank test) and in the PWS group (pre-meal: $Z = -2.67$, $p < 0.01$; post-meal: $Z = -2.37$, $p < 0.01$).

### fMRI Data

**HWC: Food vs. Non-food Response—**The primary analyses within the HWC group involved the following contrasts: 1) pre-meal: food > non-food, 2) pre-meal: non-food > food, 3) post-meal: food > non-food, and 4) post-meal: non-food > food. Within the HWC group, food images produced greater activation than non-food images before eating in the right lateral OFC, left posterior OFC, right medial PFC, and bilateral fusiform gyrus, whereas non-food images elicited greater activation than food in the posterior fusiform gyrus/cerebellum (Table 1). After eating, individuals in the HWC group responded to a greater degree to food than non-food images in the left posterior OFC and bilateral fusiform gyrus, whereas non-food images elicited greater response in the bilateral fusiform gyrus (Table 2). Post hoc regions are listed in Tables 1 and 2.

**PWS: Food vs. Non-food Response—**This primary set of analyses within the PWS group involved the following contrasts: 1) pre-meal: food > non-food, 2) pre-meal: non-food > food, 3) post-meal: food > non-food, and 4) post-meal: non-food > food. Within the PWS group, there were no a priori regions exhibiting greater activation to food than non-food before eating. However, greater activation to non-food images than food images before eating was exhibited in the fusiform gyrus (Table 3). In comparison, this group displayed greater activation to food than non-food images after eating in the bilateral medial PFC, bilateral insula, left hippocampus, left parahippocampal gyrus, and right fusiform gyrus (Table 4). Post hoc regions

are listed in Tables 3 and 4. There were no regions showing greater non-food than food activation after eating.

**HWC Group: Pre-meal vs. Post-meal Response—**To confirm activation to food in a priori regions, we performed an additional set of analyses examining activation to food vs. low-level baseline. Within the HWC group, we examined the following contrasts: 1) pre-meal > post-meal response to food (vs. baseline) and 2) post-meal > pre-meal response to food (vs. baseline). Results from the first contrast indicate that individuals in the HWC group exhibited greater response to food pre-meal than post-meal in the right amygdala, bilateral OFC, left frontal operculum, and left fusiform gyrus. The second contrast yielded greater activation post-meal compared with the pre-meal in the medial PFC; notably, there was no activation to food in the amygdala in this group after the meal.

**PWS Group: Pre-meal vs. Post-meal Response—**Within the PWS group, we examined the following contrasts: 1) pre-meal > post-meal response to food (vs. baseline) and 2) post-meal > pre-meal response to food (vs. baseline). Results from the first contrast revealed no regions of activation. However, greater activation post-meal than pre-meal was exhibited in the bilateral OFC, bilateral medial PFC, bilateral insula, and left fusiform gyrus.

**PWS vs. HWC Group Interaction: Pre-meal Response—**Finally, to obtain a more direct comparison of group differences in activation in response to food vs. baseline during the pre-meal condition, we conducted an interaction analysis with the following contrasts: 1) HWC > PWS response to food (vs. baseline) and 2) PWS > HWC response to food (vs. baseline). Results from the first contrast confirmed greater activation in a priori regions in the HWC group than in the PWS group before eating, including bilateral OFC (*x*,*y*,*z* coordinates: 25,34, − 4; −26,36,−4), medial PFC (37,30,26; −26,42,29), insula (46,12,8; −32,12,11), parahippocampal gyrus (16,−30,−4; −14,−30,−4), and right fusiform gyrus (28,−45,−7). Results from the second contrast (PWS > HWC) yielded no regions of activation.

**PWS vs. HWC Group Interaction: Post-meal Response—**For the post-meal condition, no regions of activation were noted for the HWC > PWS food vs. baseline contrast. However, the PWS > HWC contrast revealed that, after eating, the PWS group exhibited greater activity to food images compared with the HWC group in the right amygdala (22,− 9,−16), right OFC (40,21,−10), bilateral medial PFC (4,54,35; −26,7,62), bilateral insula (40,−18,17; −38, −15, −1), left parahippocampal gyrus (−17, −33, −10), and right fusiform gyrus (44, −42, −16) (Figure 1).

## Discussion

This study used fMRI to examine the neural basis of hyperphagia in PWS. Results provide evidence that individuals with PWS display different patterns of neural activity in response to food stimuli compared with a group of typically developing healthy-weight individuals. These differences may contribute to the characteristic failures of satiation observed in PWS. Results in the PWS group suggest that neural systems involved in food motivation are disrupted to the extent that satiation mechanisms may fail to operate normally; in fact, results in the PWS group were most atypical after eating. Direct contrasts between groups suggest that the PWS group exhibited significantly different responses to food both during pre-meal (decreased in comparison to HWC) and post-meal (increased in comparison to HWC) states in the amygdala, OFC, medial PFC, insula, parahippocampal gyrus, and fusiform gyrus. These areas normally decrease in response to food after eating (26,28,35).

The regions of interest exhibiting abnormal patterns of activation in the PWS group are part of the network associated with affect-driven motivation: the limbic system and paralimbic

cortex. Lesion studies in primates indicate that the amygdala is necessary for learning cues associated with satiation (36) and the ability to compete for food (37). More recent neuroimaging studies confirm this connection between the amygdala and food intake, showing differential activity in the amygdala in response to food stimuli in the context of varying caloric levels of food stimuli (38) or during hunger vs. satiation states (25,26). These increases in activation during hunger and in response to higher calorie foods show the amygdala's motivational response that might lead to approach behaviors (i.e., eating while hungry) as opposed to less motivational responses that would lead to avoidance behaviors (i.e., failing to consume foods when satiated). Our results in the HWC group are consistent with this theory, with greater activation to food pre-meal than post-meal in the amygdala. In comparison, the PWS group exhibited greater activation than the HWC group in the amygdala after eating.

The OFC is believed to play a role in stimulus-reinforcement learning (39), with extensive connections to the amygdala that have been implicated in affect-driven motivational behavior (40–42). In addition to integration of information from multiple sensory inputs, the OFC serves a role in reward learning. The PWS group exhibited greater food-related activation post-meal than pre-meal in the OFC, with greater activation post-meal than the HWC group, indicating dysfunction in the reward-learning circuit in the PWS group. The medial PFC is reciprocally connected to the amygdala, OFC, and hypothalamus in the primate brain and is, therefore, in a position to mediate communication between the highly reward-based, affective OFC (43) and more cognitive realms of the lateral PFC (44) in a highly motivational context. In our study, individuals with PWS exhibited greater activity to food than the HWC group in both lateral and medial PFC regions after eating.

While the hypothalamus plays a central role in the regulation of energy homeostasis, we did not identify distinct patterns of activation related to pre- and post-meal states within this structure in either the PWS or HWC groups. However, our lack of findings in the hypothalamus does not rule out this region's central role in food motivation. Imaging of the hypothalamus using fMRI may require paradigm designs and imaging scans that specifically detect longer duration changes characteristic of this structure in response to glucose ingestion. For example, Liu et al. (45) used temporal clustering analysis and fMRI to identify regions of maximal response in the hypothalamus by combining signal intensity, timing, and spatial extent over a 48-minute scan. More recently, Shapira et al. (24) used this paradigm to document altered hypothalamic response in individuals with PWS.

While obesity and extreme overeating have been recognized as core phenotypic features of PWS, investigators studying PWS are only beginning to examine potential relationships between PWS and obesity in the general population. Behaviorally, individuals with PWS display an exaggerated form of hunger and hyperphagia not seen in other groups. In contrast, despite normal or only mildly elevated levels of hunger, individuals with obesity generally exhibit excessive caloric intake with reference to the amount needed for normal energy balance (46). There may also be hormonal differences between individuals with PWS and those with obesity in the general population. For instance, individuals with PWS have very high plasma ghrelin levels, whereas low systemic ghrelin levels are reported in non-PWS obesity (23).

To date, neuroimaging findings in obesity are inconsistent, possibly because of variability in methodology (i.e., single photon emission computed tomography, $^{15}$O- and fluorodeoxyglucose-positron emission tomography, fMRI). In general, comparisons between neuroimaging studies of obesity and current findings in PWS indicate areas of both similarity and difference. For example, current results coincide well with neural patterns seen in a recent positron emission tomography study of obese men, who displayed greater increases in PFC activation during satiation than a control group (31). In contrast, however, Gautier et al. (31) reported decreases during satiation in the OFC, insula, and temporal pole, regions that increased

in activity post-meal in the PWS group in our study. Our results in PWS also diverge from findings of DelParigi et al. (47), who reported that regional cerebral blood flow in the amygdala, hippocampus, and posterior cingulate gyrus decreased to a greater degree in obese individuals compared with lean individuals after a meal. In contrast, the PWS group in this study exhibited increases in activation in these regions after a meal.

Results from this study are consistent with the one published study using fMRI to study individuals with PWS. Although Shapira et al. (24) used a different methodology to examine hyperphagia in PWS, both studies found greater activation in the PFC and insula [which contains the primary taste cortex (41)] after ingestion of food. While findings from this study and those reported by Shapira et al. (24) are preliminary, both suggest dysregulation of neural mechanisms in emotional control regions in PWS, lending support to the theory that hyperphagia in PWS results from lack of satiation resulting from neural dysfunction.

Some limitations of our study should be noted. First, the small sample size and use of fixed effects analytic methods limit the generalization of our findings. Future studies should use larger sample sizes, allowing more robust statistical approaches, including random effects modeling. Second, we did not attempt to match our meal sizes to each subject's BMI and corresponding caloric homeostatic needs. We modeled our meal size according to restricted dietary plans typical for individuals with PWS. However, this may have influenced the level to which each individual felt satiated, affecting patterns of activation. Furthermore, this study did not include a BMI-matched control group of obese individuals without PWS. This design limits our ability to definitively determine whether our findings arise from genetic differences or from obesity per se. Thus, although informative, we cannot be sure that our findings will generalize to obesity in the general population. Finally, subjects were not matched on handedness or IQ. However, handedness primarily affects lateralization of function (48), which was not the focus of this study. In most cases, activations were observed bilaterally. Although the lower IQ level in the PWS group may have confounded our findings, behavioral results from both groups indicate greater-than-chance performance on the memory task, suggesting that both groups were able to perform the task. Future studies should attempt to match subjects on both handedness and IQ level.

In conclusion, our findings offer initial evidence of aberrant neural responses to visual food stimuli both before and after eating a meal in a group of individuals with PWS. The PWS group exhibited large increases in response to visual food stimuli after eating in several limbic and paralimbic regions. These results further the understanding of neural mechanisms underlying extreme hyperphagia in PWS and may also provide clues regarding the underpinnings of obesity in the general population.

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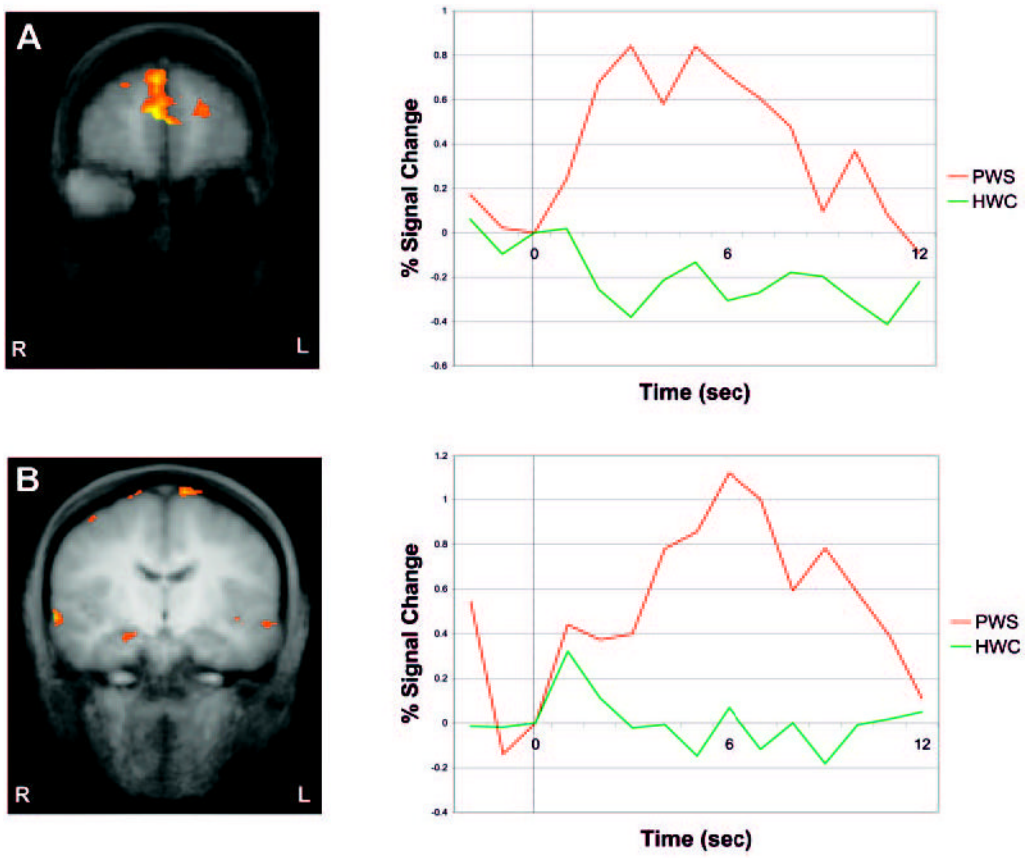


**Figure 1.**
Regions of interest analysis: results of the food vs. baseline contrast in the post-meal condition, comparing patterns of activation in HWC and PWS groups. Results are depicted in the coronal perspective, centered on (A) the medial PFC (4,54,35) and (B) the amygdala (22,−9,−16). Event-related averaging of all time-points across all blocks, separately for each group, is depicted to the left. PWS group participants (red) showed greater activation to food stimuli than the HWC group (green) for regions of interest in the medial PFC and in the right amygdala after eating.

**Table 1**

Regions reaching significance for the within-group (healthy-weight control group) analysis contrast between food and non-food stimuli categories in the pre-meal state

| Contrast and region | Brodmann's area | Coordinates | | | *t* |
|---|---|---|---|---|---|
| | | *x* | *y* | *z* | |
| Pre-meal: food > non-food | | | | | |
| Lateral orbitofrontal cortex | 47 | 46 | 24 | −7 | 6.56 |
| | 47 | 34 | 33 | −7 | 5.80 |
| Posterior orbitofrontal cortex | 47 | −26 | 30 | −4 | 7.68 |
| Medial prefrontal cortex | 10 | 7 | 51 | 20 | 6.04 |
| | 10 | 7 | 54 | 11 | 6.11 |
| | 10 | 16 | 54 | 15 | 5.71 |
| Fusiform gyrus | 37 | 25 | −52 | −10 | 8.81 |
| | 37 | −29 | −51 | −10 | 8.99 |
| Superior temporal gyrus | 21 | 64 | −15 | 2 | 6.26 |
| Inferior parietal lobule | 40 | −65 | −27 | 29 | 6.81 |
| Pre-meal: non-food > food | | | | | |
| Fusiform gyrus/cerebellum | | 37 | −48 | −22 | −8.71 |
| | | −38 | −48 | −19 | −10.42 |

$p < 0.01$, corrected for whole brain.

**Table 2**

Regions reaching significance for the within-group (healthy-weight control group) analysis contrast between food and non-food stimuli categories in the post-meal state

| Contrast and region | Brodmann's area | Coordinates | | | *t* |
|---|---|---|---|---|---|
| | | *x* | *y* | *z* | |
| Post-meal: food > non-food | | | | | |
| Posterior orbitofrontal cortex | 47 | −23 | 24 | −7 | 7.34 |
| Fusiform gyrus/cerebellum | | 25 | −54 | −10 | 7.07 |
| | | −29 | −54 | −10 | 8.55 |
| Post-meal: non-food > food | | | | | |
| Fusiform gyrus | 37 | 40 | −51 | −16 | −7.18 |
| | 37 | −38 | −48 | −16 | −7.58 |
| Superior frontal gyrus | 6 | −20 | 18 | 59 | −5.95 |
| | 9 | −17 | 61 | 29 | −6.78 |
| | 8 | −17 | 39 | 50 | −5.89 |

$p < 0.01$, corrected for whole brain.

**Table 3**

Regions reaching significance for the within-group (Prader-Willi syndrome group) analysis contrast between food and non-food stimuli categories in the pre-meal state

| Contrast and region | Brodmann's area | Coordinates | | | *t* |
|---|---|---|---|---|---|
| | | *x* | *y* | *z* | |
| Pre-meal: food > non-food | | | | | |
| Inferior prefrontal cortex | 45 | 55 | 33 | 2 | 6.55 |
| Superior temporal gyrus | 38 | −26 | 15 | −37 | 6.18 |
| Middle temporal gyrus | 21 | 43 | 9 | −31 | 6.14 |
| Superior frontal gyrus | 6 | −14 | 12 | 65 | 5.59 |
| Cerebellum | | 22 | −66 | −16 | 5.84 |
| Pre-meal: non-food > food | | | | | |
| Fusiform gyrus | 18 | 37 | −75 | −10 | −6.70 |
| | 37 | 37 | −48 | −19 | −9.59 |
| | 36 | −38 | −21 | −13 | −7.60 |
| Inferior prefrontal cortex | 47 | 31 | 18 | −16 | −5.40 |
| Anterior cingulate cortex | 24 | 4 | 24 | −4 | −5.55 |
| Medial temporal gyrus | 37 | −53 | −60 | 2 | −6.37 |
| Inferior parietal lobule | 40 | −56 | −51 | 38 | −6.20 |
| Middle occipital gyrus | 19 | −47 | −76 | −7 | −6.44 |
| Cerebellum | | 37 | −48 | −19 | 9.59 |
| | | −38 | −45 | −25 | −9.63 |

$p < 0.01$, corrected for whole brain.

**Table 4**

Regions reaching significance for the within-group (Prader-Willi syndrome group) analysis contrast between food and non-food stimuli categories in the post-meal state

| Contrast and region | Brodmann's area | Coordinates | | | *t* |
|---|---|---|---|---|---|
| | | *x* | *y* | *z* | |
| Post-meal: food > non-food | | | | | |
| Medial prefrontal cortex | 8 | −17 | 27 | 41 | 5.81 |
| | 8 | −29 | 27 | 41 | 5.48 |
| | 10 | −11 | 51 | 14 | 5.75 |
| | 46 | 40 | 42 | 14 | 5.44 |
| Insula | | 32 | −11 | 18 | 5.88 |
| | | −35 | −3 | 17 | 5.71 |
| | | −38 | −18 | 2 | 5.60 |
| Hippocampus | | −31 | −35 | −6 | 6.75 |
| | | −28 | −23 | −12 | 5.87 |
| Parahippocampal gyrus | 29 | −14 | −39 | −1 | 6.34 |
| Fusiform gyrus | 19 | 22 | −57 | −10 | 7.72 |
| Superior frontal gyrus | 6 | 13 | −3 | 65 | 6.13 |
| | 9 | 10 | 51 | 35 | 6.58 |
| Medial temporal gyrus | 21 | 43 | 9 | −28 | 6.00 |
| | 21 | −41 | 9 | −28 | 5.36 |
| Inferior temporal gyrus | 19 | −53 | −63 | −1 | 6.93 |
| Superior temporal gyrus | 38 | −35 | 18 | −25 | 5.37 |
| Transverse temporal gyrus | 41 | −35 | −27 | 17 | 5.66 |
| Uncus | 28 | 22 | 9 | −20 | 5.53 |
| Putamen | | 19 | 18 | −4 | 5.63 |
| Supramarginal gyrus | 40 | −50 | −27 | 29 | 6.17 |
| | 40 | −38 | −57 | 47 | 6.77 |
| Postcentral gyrus | 1 | 58 | −24 | 38 | 6.19 |
| Precuneus | 7/19 | 13 | −78 | 41 | 6.48 |
| Cerebellum | | −23 | −63 | −16 | 7.31 |
| | | 22 | −39 | −34 | 6.05 |
| Post-meal: non-food > food | | | | | |
| None | | | | | |

$p < 0.01$, corrected for whole brain.