PAPER

Enhanced activation of reward mediating prefrontal regions in response to food stimuli in Prader–Willi syndrome

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Background: Individuals with Prader–Willi syndrome (PWS) exhibit severe disturbances in appetite regulation, including delayed meal termination, early return of hunger after a meal, seeking and hoarding food and eating of non-food substances. Brain pathways involved in the control of appetite in humans are thought to include the hypothalamus, frontal cortex (including the orbitofrontal, ventromedial prefrontal, dorsolateral prefrontal and anterior cingulate areas), insula, and limbic and paralimbic areas. We hypothesised that the abnormal appetite in PWS results from aberrant reward processing of food stimuli in these neural pathways.

Methods: We compared functional MRI blood oxygen level dependent (BOLD) responses while viewing pictures of food in eight adults with PWS and eight normal weight adults after ingestion of an oral glucose load.

Results: Subjects with PWS demonstrated significantly greater BOLD activation in the ventromedial prefrontal cortex than controls when viewing food pictures. No significant differences were found in serum insulin, glucose or triglyceride levels between the groups at the time of the scan.

Conclusions: Individuals with PWS had an increased BOLD response in the ventromedial prefrontal cortex compared with normal weight controls when viewing pictures of food after an oral glucose load. These findings suggest that an increased reward value for food may underlie the excessive hunger in PWS, and support the significance of the frontal cortex in modulating the response to food in humans. Our findings in the extreme appetite phenotype of PWS support the importance of the neural pathways that guide reward related behaviour in modulating the response to food in humans.

Prader–Willi syndrome (PWS) is the most commonly recognised genetic cause of childhood obesity. Approximately 70% of PWS cases are due to a genetic deletion on chromosome 15 (15q11–13), 25% of PWS cases are from a maternal uniparental disomy of chromosome 15 and the remaining cases result from imprinting defects.^{1–2} This syndrome is characterised by infantile hypotonia, mental retardation, short stature, hypogonadism, hyperphagia and early onset obesity.³ The early onset morbid obesity is the most significant health problem experienced by individuals with PWS, as it is their primary cause of morbidity and mortality.

Individuals with PWS typically have failure to thrive in infancy, which is followed by the onset of obesity at the age of 18–36 months, usually without a significant change in calories. Subsequently, these patients develop significant hyperphagia which worsens the obesity. By adulthood, significant hyperphagia is present in almost all individuals with PWS. These individuals may steal and hoard food, eat non-food substances (pica behaviour) and, if given free access to food, will consume three to six times as much food as control subjects.^{4–5} The hyperphagia appears refractory to psychopharmacological intervention. Additionally, individuals with PWS have delayed meal termination and earlier return of hunger after a previous meal.⁴ These appetite disturbances are thought to be primarily due to hypothalamic dysfunction, given the other hypothalamic abnormalities in PWS, including growth hormone deficiency, hypogonadotropic hypogonadism and temperature dysregulation.⁶ Indeed, a reduction in the number of cells in the paraventricular nucleus, including anorexigenic oxytocin neurons, has been seen in post-mortem hypothalami.⁷

While plasma levels of leptin, an anorexigenic hormone produced by adipose tissue, are appropriately elevated in PWS,

multiple studies have shown other metabolic and hormonal abnormalities in PWS that may contribute to their hyperphagia.^{8–12} However, the relative importance of these abnormalities and their relationship to brain defects in PWS remains unclear.

As PWS represents an extreme appetite phenotype, study of this population could help elucidate the biological and neuroanatomical pathways that control appetite in humans and lead to a greater understanding of the pathophysiology of obesity. In vivo functional neuroimaging has recently been used to study the brain pathways involved in human appetite control.¹³ Positron emission tomography (PET) studies have highlighted changes in neuronal activity, as measured by regional resting cerebral blood flow, between fasted and fed states in several brain regions that may mediate satiety, including the hypothalamus, orbitofrontal cortex, insula and inferotemporal cortex, and limbic and paralimbic areas.¹³ The inter-relationship of these areas is thought to be involved in reward, arousal, motivational, memory and emotional responses to food and eating. Both PET and functional MRI (fMRI) studies have demonstrated acute regional activity changes in these brain regions in response to food stimuli strongly supporting a role for the frontal cortex in the reward responses to food in healthy subjects.^{14–17}

In a previous study using fMRI, we found that individuals with PWS showed a temporal delay in the resting hypothalamic and frontal cortex response to glucose ingestion (25 min) compared with both normal weight (10 min) and obese controls (15 min).¹⁸ We hypothesise that the increased appetite in PWS arising from neuroendocrine, particularly hypothalamic, defects

Abbreviations: BOLD, blood oxygen level dependent; fMRI, functional MRI; PET, positron emission tomography; PWS, Prader–Willi syndrome

Table 1 Prefrontal cortex blood oxygen level dependent responses by group and stimulus category

Contrast	Foci coordinates (mm Talairach)			Max t value	Cluster size (mm ³) ($t > 4$)
	x	y	z		
PWS vs controls					
Food vs rest	-11	48	2	5	437
	14	28	-3	5.4	208
Tool vs rest	-	-	-	-	-
PWS					
Food vs rest	-7	51	0	7.2	1217
Tool vs rest	5	36	-5	5.8	192
Controls					
Food vs rest	32	29	-2	5.1	190
	-25	29	0	4.4	60
Tool vs rest	-	-	-	-	-

PWS, Prader-Willi syndrome.

results in abnormal reward processing in the brain that predisposes to excess caloric intake. This study, therefore, investigated the reward responses to food stimuli in PWS by using fMRI to evaluate the blood oxygen level dependent (BOLD) responses to food pictures in individuals with PWS compared with normal weight sibling controls after ingestion of an oral glucose load.

METHODS

Participants

Study participants were a subsample from an investigation of neuroanatomical variability in PWS across the lifespan. Only adult participants over 18 years of age were included in this fMRI study. One participant with PWS was excluded for inability to quietly view visual stimuli. Sixteen remaining participants were able to perform the task without excessive head motion (>1 mm/min). Eight participants were individuals with PWS (PWS group; mean (SD) age 25 (8.3) years; two females, six males) and eight were healthy siblings of PWS patients (control group; mean (SD) age 27 (7.0) years; four female, four male).

Molecular testing was done on all PWS subjects.¹ Five PWS participants had a deletion of the chromosomal 15q11–13 region while the remaining three had maternal uniparental disomy of chromosome 15. Subjects with PWS were significantly more obese than controls, as assessed by body mass index (33.1 (3.2) vs 24.8 (1.4); $p = 0.02$). None of the PWS patients were being treated with growth hormone or oestrogen/androgen replacement at the time of this study. The protocol was approved by the Institutional Review Board at the University of Florida and informed consent was obtained from the participants and their legal guardians.

Neuroimaging

Anatomical brain images were acquired from participants using a 3T head dedicated Siemens Allegra MRI scanner (Siemens, Munich, Germany). Anatomical scanning included a three dimensional T1 scan using an MPRAGE sequence with matrix 512 × 512, TR 1500 ms, TE 4.38 ms, FOV 240 mm, FA 8° and 160

contiguous slices (1.1–1.4 mm thick, no gaps). Prior to scanning, participants received a glucose load of 75 g to mimic a postprandial metabolic state. After a suitable delay allowing sufficient time for gastric emptying ($t_{1/2}$ has been reported as 103 min for individuals with PWS and 63 min for controls) and for maximal changes in resting BOLD signal to occur in each group (10 min in control subjects, 25 min in PWS subjects),^{18, 19} participants were returned to the scanner for echo-planar functional imaging with the following parameters: matrix 64 × 64, TR 3 s, TE 25 ms, FA 90°, FOV 240 mm, 36–40 axial slices of 3.8 mm thickness (no gaps). During echo-planar imaging, participants viewed images of food, animals and tools selected from the International Affective Picture System.²⁰ Standardised ratings of valence and arousal were significantly less for tools stimuli than other stimuli ($p < 0.001$) but did not differ between food and animal stimuli (tables 1, 2). Stimuli were presented by block design with the IFIS system (MRI Devices; Gainesville, Florida, USA). Blocks lasted 30 s, with five picture stimuli per block (5 s per stimulus and 1 s interstimulus interval). Category blocks were separated by a 9 s rest period. Each session was also accompanied by an extended resting period (see below). During rest periods, participants viewed a fixation point centred on a black screen.

Two block designs were used for stimulus presentation. Participants in the first design viewed six blocks of food, four blocks of tools and two blocks of animals, with a 75 s resting block. Participants in the second design viewed four blocks of food, two blocks of tools and two blocks of animals with a longer resting period (3 min) to improve future analysis of resting connectivity. For the current study, picture categories and rest blocks from both designs were combined for statistical analysis.

All functional data analyses were performed in BrainVoyager 2000 (Brain Innovations, Maastricht, The Netherlands). Functional images were coregistered with anatomical images and transformed into Talairach space before undergoing motion correction, linear trend removal and Gaussian spatial smoothing (FWHM 6 mm). A fixed effects general linear model analysis²¹ was performed on all brain regions with three factors: block (food, animal, tools or rest), group (PWS or control) and Subject. This general linear model identified voxels within each participant group whose activities during stimulus blocks significantly differed from rest, as well as voxels whose activities significantly differed across groups (ie, block × group interaction). Cluster analysis was then performed to find clusters (exceeding 50 mm³ in volume) of voxels whose uncorrected absolute t scores exceeded an a priori threshold of 4. Corrections for multiple comparisons were not performed as the Bonferroni corrections performed by BrainVoyager 2000

Table 2 Valence and arousal descriptives by category

Category	Valence	Arousal
Food	7.02 (0.39)	4.87 (0.23)
Animals	6.98 (0.62)	4.12 (1.03)
Tools	5.01 (0.17)	2.69 (0.37)

Data are mean (SD).

Figure 1 Frontal cortex activation to food stimuli by participant group. The fixed effects general linear model (GLM) contrast of food versus rest indicated significantly greater ventromedial prefrontal cortex activation for both the control and Prader–Willi syndrome (PWS) groups. The statistical maps depict all voxels with $|t|$ values exceeding 4. Blood oxygen level dependent activity clusters are indicated by white arrows in each group.

tend to be too conservative for functional neuroimaging analyses.²²

Hormonal and metabolic measurements

Serum was collected during fasting and at the time of the fMRI scan in serum separator tubes. All hormonal measurements were performed using standardised protocols in our hospital laboratory. Serum insulin was measured by enzyme immunoassay on a Roche 2010 Analyser, glucose using the enzymatic glucose oxidase method on the Roche Integra Analyser and triglycerides using end point chemistry after enzymatic hydrolysis on the Roche Integra Analyser (Basel, Switzerland).

RESULTS

The general linear model identified voxels whose activities significantly differed ($|t| > 4$) between any stimulus viewing condition and rest. Table 1 describes the volume (in mm^3) and magnitude (as maximum $|t|$) for clusters of prefrontal cortex voxels. The observed prefrontal activations encompassed aspects of both the ventromedial prefrontal and subcallosal cingulate cortices. Susceptibility artefact ablated functional imaging of the orbitofrontal cortex, thus forming an artefactual anterior border to activation. We found no significant differences in activity in these frontal regions for comparisons not listed in table 1 (eg, food vs tools or animal vs rest).

Statistical parametric maps were generated to graphically depict differences between the food versus rest condition for each participant group (fig 1). Figure 1 shows the regions of activation described in table 1, along with voxels in other regions (eg, visual cortex) with t score thresholds exceeding 4. Individuals with PWS demonstrated a markedly larger prefrontal cortex response to food pictures than normal weight controls. Figure 2 depicts this difference with an across group general linear model analysis. Figures 1 and 2 show the axial slices bearing each cluster's statistical foci. The focus of the BOLD activation in individuals with PWS was more anterior and medial than observed for control participants, whose activity bordered the lateral prefrontal cortex.

Activation of the frontal cortex was also observed for the tool versus rest contrast in PWS but not in control subjects (table 1). Similar to the food versus rest contrast, tools versus rest yielded a cluster that was also focused in the frontal cortex. No other contrast elicited significantly different frontal cortex activity. However, the enhanced ventromedial prefrontal activation observed in individuals with PWS was also accompanied by a significantly diminished BOLD response in the visual cortex relative to controls (figs 1, 2). Subsequent visual testing indicated no difference in visual acuity between groups.

Hormonal measurements

Serum insulin and glucose levels increased significantly compared with fasting values by the time of the fMRI scan in both groups ($p < 0.01$ for both groups) but triglyceride levels did not change significantly ($p = 0.67$). However, no significant differences were seen in serum insulin, glucose or triglycerides between PWS patients and controls, when fasted or at the time of the fMRI scan, suggesting similar metabolic milieus in response to the glucose load across groups at the time of the scanning (table 3).

DISCUSSION

Individuals with PWS demonstrated significantly greater prefrontal cortex activity than lean controls when viewing pictures of food following an oral glucose load. This response is consistent with a heightened reward response in PWS to food even after adequate time allowed for the resting brain to respond to the hormonal and metabolic changes that occur after ingestion of glucose. The enhanced ventromedial prefrontal cortex response to food stimuli suggests that an increased reward value for food may lie behind the excessive hunger in PWS, and supports the importance of the frontal cortex in mediating the hunger and satiety response in humans. PWS subjects also demonstrated significantly decreased BOLD responses in the visual cortex relative to controls; this double dissociation between the frontal cortex and visual cortex

Figure 2 Differential frontal cortex activation of the Prader–Willi vs syndrome (PWS) and control groups to food stimuli. A fixed effects general linear model analysis contrasted blood oxygen level dependent response to food stimuli across participant groups. PWS patients demonstrated significantly greater ventromedial prefrontal cortex activation (cluster centre $-11, 48, 2$ mm Talairach, shown in orange) than controls, despite significantly diminished visual cortex activation (cluster centre $-2, -85, -12$ mm Talairach, shown in blue). A, anterior; R, right side; S, sagittal.

Table 3 Laboratory values: fasting and at the time of the functional MRI scan

Subjects	Fasting	fMRI	Fasting	fMRI	Fasting	fMRI
	Insulin (μ U/ml)	Insulin (μ U/ml)	Glucose (mg/dl)	Glucose (mg/dl)	Triglycerides (mg/dl)	Triglycerides (mg/dl)
Controls	9 (6)	41 (107)	86 (12)	116 (119)	108 (65)	100 (44)
PWS	6 (18)	26 (64)	83 (39)	122 (90)	102 (28)	105 (28)
t test PWS vs controls	p = 0.29	p = 0.35	p = 0.72	p = 0.71	p = 0.78	p = 0.78

fMRI, functional MRI; PWS, Prader–Willi syndrome.
All data are mean (SD).

responses excludes the possibility that PWS patients have globally heightened BOLD responses that are not specific to the frontal cortex.

The length of the resting baseline was expanded during the course of this study to improve the power of future resting connectivity analyses. As previously mentioned, design No 1 had six food, four tool and two animal blocks, with a resting baseline of 75 s, while design No 2 had four food, two tool and two animal blocks, with a resting baseline of 180 s. Design No 1 had more participants with PWS (7/8) than control participants (4/8), indicating a potential confounding factor. This possibility was addressed by comparing the prefrontal responses of control participants to food stimuli between both designs. No significant differences were found across designs, even at liberal thresholds ($|t| > 1.5$, $p < 0.13$), indicating that the diminished prefrontal cortex response of the normal weight controls relative to individuals with PWS was not caused by differences in experimental design.

We were unable to directly measure activity in the orbitofrontal cortex area of the frontal cortex because of susceptibility artefact (fig 3). However, our findings of increased BOLD activation in the frontal cortex are consistent with those from a recent PET study showing that PWS subjects scanned while choosing food items after a meal lacked the normal changes in the orbitofrontal cortex resting cerebral blood flow observed in a previous study of normal weight subjects.^{17–23} Our findings are also in agreement with a recent

fMRI study comparing children with PWS to normal weight controls, which found increased activation of the medial prefrontal cortex bilaterally in subjects with PWS when viewing food pictures after eating a mixed meal.²⁴

The frontal cortex has been implicated in the representation of emotional stimuli, assignment of emotional valence/salience to stimuli, stimulus–reinforcement association learning, motivation and socioemotional control.²⁵ Through the use of fMRI, the frontal cortex has been found to link food and other types of reward with hedonic experience,²⁶ and is also thought to be involved in sensory integration, representation of affective value as well as decision making and expectation.²⁷ The frontal cortex has been shown to represent not only the reward value and expected reward value of foods and other reinforcers but also their subjective pleasantness.²⁷ It is hypothesised that the system for predicting rewards and guiding behaviour lies within the interactions of several areas of the brain, including the anterior cingulate, insula, amygdala and frontal cortex.²⁸ This motivational/reward system is also responsible for integrating autonomic responses to stimuli and mapping visceral responses in the brain.²⁸ Specifically, both the subcallosal cingulate and the ventromedial prefrontal cortex monitor signals from the viscera and guide reward related behaviours.^{29–30} These regions perform internal monitoring while at rest, and demand attentional resources to do so,³¹ and, as such, the increased activation of these areas in individuals with PWS in response to viewing food related pictures suggests a strong emotional response to the images in these individuals. Thus this motivational/reward system in the brain may contribute to the pathological increase in food consumption in PWS by overriding hormonal signals of satiety.

Abnormalities in hormones that effect appetite and satiety are well described in individuals with PWS.^{8–12} However, at this point there is no evidence that these hormonal abnormalities in PWS actually influence appetite and satiety.^{32–33} We have found that fasting levels of insulin, glucose and triglycerides, as well as values of these hormones at the time of the fMRI, did not differ significantly between our normal weight controls and the PWS subjects in this study. This finding suggests that these hormones and metabolites are not responsible for the differences in fMRI signal in the frontal cortex in response to food items between the controls and PWS subjects.

Activation of the frontal cortex in PWS subjects in response to tool images was unexpected but may stem from the inclusion of both food related tools (eg, spoons, cups) and non-food tools (eg, hammers, hairdryers) within the tools image set. Images of utensils associated with eating could account for the enhanced frontal cortex responses to tools in PWS patients as such activation was not seen in control subjects and there was no increased frontal cortex activation in the PWS subjects in response to viewing animal pictures. Future research would benefit by excluding food related tool stimuli or by specifically contrasting food and non-food related tools.

It remains to be determined if the differences in fMRI BOLD activation in the frontal cortex in PWS subjects is a result of

Figure 3 Artefact induced ablation of the orbitofrontal blood oxygen level dependent response. (Top) The orbitofrontal cortex was manually drawn in sagittal slices atop a template MPRAGE anatomical brain image. (Bottom) The echo planar images of all 16 participants were visually inspected for overlap of functional images with anatomically defined orbitofrontal cortex. The functional scan of the subject with the median amount of overlap (approximately 30%) is depicted.

hormonal-hypothalamic abnormalities or developmental defects in other brain regions. At present, little is known about the structural development of the frontal cortex. However, as PWS is a contiguous gene syndrome that results in the loss of expression of several imprinted genes on chromosome 15 which are normally expressed in the brain, there may be abnormal development of the frontal cortex in addition to other brain regions.¹⁻³ Our group has found that individuals with PWS have many previously undescribed structural abnormalities in the brain, including abnormalities of the insular cortex.³⁴

The small sample size in this study and the lack of a matched obesity control group are limitations of the study. As such, we did recruit age and sex matched obese controls who were matched by DEXA percentage body fat to the individuals with PWS but the majority of these individuals were not able to lie comfortably in the scanner because of a large neck circumference and broad shoulder span. Future studies will need to address these issues by including a larger number of individuals with both PWS and non-syndromal obesity.

We have identified enhanced prefrontal cortex activation to visually presented food stimuli in subjects with PWS compared with normal weight controls. These differences in frontal cortex activation appear specific to food stimuli, independent of insulin, glucose and triglyceride levels. Therefore, our findings contribute to the understanding of the pathophysiology of the hyperphagia which is present in individuals with PWS and demonstrate the potential importance of the frontal cortex in the reward response to food.

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