An investigation into food preferences and the neural basis of food-related incentive motivation in Prader–Willi syndrome

E. C. Hinton,1 A. J. Holland,1 M. S. N. Gellatly,2 S. Soni1 & A. M. Owen3

1 Section of Developmental Psychiatry, Department of Psychiatry, University of Cambridge, Cambridge, UK
2 The Prader–Willi Syndrome Association, Derby, UK
3 MRC Cognition and Brain Sciences Unit, & the Wolfson Brain Imaging Centre, Addenbrooke’s Hospital, Cambridge, UK

Abstract

Background Research into the excessive eating behaviour associated with Prader–Willi syndrome (PWS) to date has focused on homeostatic and behavioural investigations. The aim of this study was to examine the role of the reward system in such eating behaviour, in terms of both the pattern of food preferences and the neural substrates of incentive in the amygdala and orbitofrontal cortex (OFC).

Method Participants with PWS (n = 18) were given a food preference interview to examine food preferences and to inform the food-related incentive task to be conducted during the neuroimaging. Thirteen individuals with PWS took part in the positron emission tomography (PET) study, the design of which was based on a previous study of non-obese, non-PWS controls. For the task, participants were asked to consider photographs of food and to choose the food they would most like to eat in two conditions, one of high and one of low incentive foods, tailored to each participant’s preferences. For comparison of the food preference data, 12 non-PWS individuals were given one part of the interview.

Results Individuals with PWS expressed relative liking of different foods and showed preferences that were consistent over time, particularly for sweet foods. The participants with PWS did give the foods in the high incentive condition a significantly higher incentive value than the foods in the low incentive condition. However, activation of the amygdala and medial OFC was not associated with the prospect of highly valued foods as predicted in those with PWS.

Conclusions It would appear that incentive motivation alone plays a less powerful role in individuals with PWS than in those without the syndrome. This is likely to be due to the overriding intrinsic drive to eat because of a lack of satiety in those with PWS, and the impact of this on activity in the incentive processing regions of the brain. Activity in such reward areas may not then function to guide behaviour selectively towards the consumption of high preference foods.

Keywords amygdala, food preferences, incentive motivation, orbitofrontal cortex, positron emission tomography, Prader–Willi syndrome
Introduction

Prader–Willi syndrome (PWS) is a neurodevelopmental disorder resulting from the absence of expression of the paternal copy of as yet unidentified maternally imprinted gene(s) at the genetic locus 15(q11–13). PWS is characterized by mild to moderate learning disability, hyperphagia and a preoccupation with food leading to life-threatening obesity if left uncontrolled. Research has focused on understanding the excessive eating at the level of gut hormones (e.g. Cummings et al. 2002; Goldstone et al. 2005), behavioural patterns (Zipf & Berntson 1987; Holland et al. 1993; Lindgren et al. 2000) and neural structure and function, particularly at the level of the hypothalamus (Swaab et al. 1995; Swaab 1997; Goldstone 2004; Lucignani et al. 2004). Recent neuroimaging studies have indicated that the satiety system is insensitive and delayed in people with PWS (Hinton et al. 2005; Shapira et al. 2005).

Although it has been assumed that homeostatic neural processes are likely to underlie the hyperphagia in PWS, a further corticolimbic system could also be involved, encompassing the motivational, cognitive and emotional aspects of eating behaviour (Saper et al. 2002; Berthoud 2004). For those without PWS, the reward value of food, in terms of both the hedonic pleasure of eating and the incentive to eat preferred food, is a powerful motivating factor, over and above hunger state. Such appetitive incentive motivation was previously investigated in non-obese individuals in two studies which examined the neural basis of incentive, hunger state and decision making (Arana et al. 2003; Hinton et al. 2004). By using a novel task, in which participants considered the incentive value of different meal items and chose their most preferred, it was found that activity in the amygdala and medial orbitofrontal cortex (OFC) was associated with the prospect of high incentive foods, and activity in the medial OFC was also associated with making the choice. These studies support a growing literature implicating the amygdala and OFC in identifying emotionally relevant stimuli and using this information to guide behaviour (e.g. Gottfried et al. 2003; Pickens et al. 2003).

In those with PWS, it has recently been shown that corticolimbic brain regions such as the amygdala and OFC were part of the appetitive system activated in association with fasting and food intake, in addition to the hypothalamus, striatum, temporal and anterior cingulate cortex (Hinton et al. 2005). This study provides a novel investigation into the role of these corticolimbic brain regions in terms of incentive motivational processes in those with PWS.

A key factor in deciding whether to eat a particular food is the incentive value of that food. Foods acquire an incentive value through experience: when the incentive value is high, such a food will drive behaviour towards acquisition or consumption of that food (Dickinson & Balleine 1994; Berdidge 1996). Factors such as preference, hunger state and the current environment all contribute to the incentive value of a food at any given time. These factors are also important for those with PWS: studies have shown that individuals with PWS can express food preferences, for example for sweet food (Caldwell & Taylor 1983; Taylor & Caldwell 1985; Glover et al. 1996; Rankin & Mattes 1996). Moreover, a greater preference for carbohydrates was found in one study of individuals with PWS (Fieldstone et al. 1997), but not in another (Joseph et al. 2002). Distinct preferences could be indicative of abnormalities in the underlying neurobiology; for example, it was shown in rats that specific lesions to the hypothalamus led to hyperphagia, primarily through an increase in carbohydrate consumption (Sclafani & Aravich 1983). Furthermore, an increase in appetite is often seen in those with frontotemporal dementia, in addition to an altered preference for sweet food (e.g. Snowden et al. 2001; Ikeda et al. 2002). Thus, this study incorporates an investigation into the food preferences of those with PWS, both to inform the neuroimaging study of incentive and to clarify whether individuals with this syndrome have a distinct pattern of preferences.

We predict that, given people with PWS do express food preferences, they will demonstrate a greater incentive to eat preferred foods, and that this will be associated with brain activity in the same reward areas of the brain as in those without PWS (Hinton et al. 2004). The design of this study was based on the aforementioned neuroimaging study of non-obese individuals (Hinton et al. 2004). Positron emission tomography (PET), a whole brain neuroimaging technique, was used to scan participants with PWS, while considering and choosing between high and low incentive foods, to test the hypothesis that...
increased activation in the amygdala and medial OFC would be associated with the prospect of high incentive foods. Foods were individually tailored on the basis of the responses to a food preference interview conducted prior to imaging sessions. This interview also served to examine food preferences, in terms of macronutrients (protein, carbohydrate, fat), taste (sweet, salty, bland, sour) and consistency of choices across different measures.

### Method

#### Participants

Eighteen adults with genetically confirmed PWS were recruited from local residential homes and through the Prader–Willi syndrome Association (UK) (mean age 29 years; range 18–42 years; 10 female). All participants completed the food preference interview and 13 of them took part in the imaging study. Those who were less than 21 years old, or had asthma, diabetes or severe scoliosis, or those taking olanzapine because of the known effects of weight gain were excluded from the imaging. IQ was measured for those in the imaging study (mean 70.5; range 54–88), and genetic subtype was ascertained by using previous records (12 deletion, 1 disomy) (further details of this group can be found in Hinton et al. 2005). Written, informed consent was obtained from all of the participants before commencing the study, which was approved by the Cambridge Local Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee. The comparison group for the food preference analysis consisted of 12 adults without PWS (age range 25–65 years; 8 female).

#### Measures

**Food preference interview**

The structured interview was designed primarily to ascertain food preferences to inform the imaging task. The participants with PWS were given the food preference interview prior to attending the imaging sessions. An additional section was included to assess formally food preferences according to the main macronutrient content and taste of foods. The comparison group completed only this section. In each preference trial, the participants were presented with three pictures of different foods. The foods were included according to whether they were high in protein, carbohydrate or fat in four trials (Table 1), and according to whether they had a predominantly sweet, sour, salty or bland taste in five trials (Table 1). Participants were not informed about the categories but were simply asked to choose the food they liked the most, the picture of which was then removed, and they chose their next preferred food from the remaining two. This structure is based on the methodology used in food preference literature described earlier (e.g. Caldwell & Taylor 1983).

For each trial (Table 1), the first choice food was given rank 1, the second choice food rank 2 and the third choice rank 3. The mean rank for each food type was compared by using Friedman Test in SPSS version 11.5. Where a significant difference arose, post hoc tests between specific food types were conducted by using Wilcoxon Signed Ranks Test. The same analysis was conducted with the data from the non-PWS comparison group. The responses of the two groups were compared by using Mann–Whitney U-test.

### Table 1 Food choices for each trial in the food preference interview

<table>
<thead>
<tr>
<th>Trial</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Trial</th>
<th>Sweet</th>
<th>Sour</th>
<th>Salty</th>
<th>Bland</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Beef</td>
<td>Pasta</td>
<td>Butter</td>
<td>1</td>
<td>Doughnut</td>
<td>Lemon</td>
<td>Salted corn</td>
<td>Chips</td>
</tr>
<tr>
<td>2</td>
<td>Eggs</td>
<td>Brown bread</td>
<td>Sausages</td>
<td>2</td>
<td>Cookies</td>
<td>Grapefruit</td>
<td>Plain yoghurt</td>
<td>Salted popcorn</td>
</tr>
<tr>
<td>3</td>
<td>Fish</td>
<td>Potatoes</td>
<td>Cheese</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Chicken</td>
<td>Plain rice</td>
<td>Bacon</td>
<td>4</td>
<td>Chocolate</td>
<td>Onion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>Sponge cake</td>
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</tr>
</tbody>
</table>

Food choices were made in 9 trials (4 comparing foods high in protein, carbohydrate and fat, and 5 comparing foods with different predominant tastes).

Food-related task for participants with Prader–Willi syndrome during imaging sessions

This task was based on the food-related incentive task given to the comparison group in the previous imaging study (Hinton et al. 2004). During each trial, participants were presented with three photographs of different foods with the name of the food underneath (Nelson et al. 1997). They were asked to look at each food in turn and to imagine what it would be like to eat and whether they wanted to eat it. Participants had to choose which food they would most like to eat, by touching that photograph on the screen. Trials were divided into two conditions of either high or low incentive value foods, tailored to each individual’s preferences. Foods chosen for the high incentive condition were predicted to be well liked by the participant, whereas the low incentive condition consisted of foods that the person was predicted to be indifferent to. Foods that individuals disliked were omitted in order to avoid any aversive reactions. A total of five screens could be presented during each scan. Because of the supine position of the participants in the scanner, photographs of food were presented on a monitor rather than using actual food items.

To ensure participants understood the task, a prolonged practice session was given. This entailed going through one set of pictures with the participants individually giving examples of how they should think about them by answering whether they liked the food, how it tastes and whether they wanted to eat it. They were asked not to worry about whether the food fitted into their diet plan. Three practice trials were given; the latter was completed by the participants without help and was timed with a stopwatch to give the participants an idea of how long they would have to think about the foods for each scan. All participants were able to complete the final trial without further instructions, although instructions were reiterated prior to each scan.

Post-imaging questionnaire

After the final imaging session, the participants were asked to rate from 1 to 5 each food that had been presented during the PET scans, with 1 reflecting indifference and 5 representing a high incentive value. The participants were also asked to choose their favourite from the three foods in each trial. Data from the questionnaire were analysed by using Wilcoxon Signed Ranks Test.

Consistency of responses across measures

For the PWS group only, the preference choices made in the imaging task, post-imaging questionnaire and food preference interview were compared. The number of consistent and non-consistent choices between the imaging task and the post-imaging questionnaire were compared by using chi-squared test of association ($\chi^2$). An analysis was conducted to examine whether the consistency of the choices made varied according to the IQ of the participants, using Spearman’s Rho. Judgements were made according to the IQ of the participants, using Spearman’s Rho. Judgements were made according to the IQ of the participants, using Spearman’s Rho. Judgements were made according to the IQ of the participants, using Spearman’s Rho. Judgements were made according to the IQ of the participants, using Spearman’s Rho. Judgements were made according to the IQ of the participants, using Spearman’s Rho.

Imaging acquisition and data analysis

Positron emission tomography procedures were conducted at the Wolfson Brain Imaging Centre (Addenbrooke’s Hospital, Cambridge, UK), using the GE Advance System (General Electric Medical Systems, Milwaukee, WI, USA). For each scan, 35 image slices were produced at an intrinsic resolution of approximately $4.0 \times 5.0 \times 4.5$ mm. Each participant received a 20 s intravenous bolus of $H_2^{15}O$ through a forearm cannula at a concentration of 300 MBq mL$^{-1}$ and a flow rate of 10 mL per min. Each scan provides an image of regional cerebral blood flow (rCBF) integrated over a period of 90 s from when the tracer first enters the cerebral circulation.

As part of the larger remit of this project, the imaging acquisition was split into three sessions: after participants had fasted overnight, after consuming a 400 kcal breakfast and after a 1200 kcal breakfast. The results of this manipulation are reported elsewhere (Hinton et al. 2005). During the three sessions, each participant received four consecutive scans at 8 min intervals. Half the scans in each session were high incentive trials and the other half were low incentive trials. The order of both sessions and incentive trials within each condition were counter-
balanced across participants. Two minutes and 15 s before the beginning of each scan, an instructional screen was presented to participants and the task began 15 s before the acquisition of data. Each participant was scanned in the presence of low background noise and dimmed ambient lighting. The task displays were presented on a touch-sensitive screen controlled by a Pentium microcomputer. The screen was mounted at a viewing distance so that the participant could touch all areas of the screen with the index finger of his or her right hand.

Images from the three sessions were pre-processed separately for each participant and then combined for the group statistical analysis, using SPM99 (provided by the Wellcome Department of Imaging Neuroscience, London, UK). Images within each session were realigned to the first image in that session. The images were then reoriented to the anterior commissure in order to covary out movement (Brett et al. 1999). This process created movement parameters for each session which were added into the statistical model, as a covariate of no interest, together with a scan time order covariate. The mean realigned images from the second and third imaging sessions were co-registered to the first session, and the means of the three sessions were realigned. By using the mean of the co-registered sessions, the images were normalized for global rCBF value and spatially normalized to the standard brain, based on those from the Montreal Neurological Institute, and, finally, were smoothed with a Gaussian kernel at 12 mm FWHM.

A number of anatomically specific a priori hypotheses were made based on PET imaging findings comparing high and low incentive in those without PWS (Arana et al. 2003; Hinton et al. 2004). Specifically, relatively greater activation was predicted in the amygdala and the medial OFC when testing the main effect of incentive (High–Low). Small volume corrections were applied by using regions of interests in the amygdala and medial OFC, the details of which have been reported previously (Hinton et al. 2004). The interaction between incentive and food intake was also examined. All scans were included in the analysis to investigate the interaction between the conditions of high and low incentive, and fasting, 400 kcal and 1200 kcal meals [(High: Fast–400 kcal–1200 kcal)– (Low: Fast–400 kcal–1200 kcal)]. In line with the results from Hinton et al. (2004), activation was predicted in the OFC for this interaction. For the rest of the brain, an exploratory search was conducted, so the statistical threshold for reporting a peak as significant was set at $P < 0.05$, corrected for multiple comparisons across the whole brain.

## Results

### Consistency of responses across measures

A prerequisite of the study was that those with PWS showed consistent food preferences across the different measures used. This analysis examined whether those with PWS could express preferences reliably over time and whether the measures could be considered to have validity. The percentage of consistent choices of the PWS group across the food preference interview, the choices made during the imaging task and on the post-imaging questionnaire is shown in Table 2. The average interval between the initial food preference interview and the imaging sessions was 17 weeks (range 0–44 weeks). The interval between the measurements did not correlate with the consistency of the responses between the food preference interview and the imaging task (Spearman’s $\rho = 0.166$, $P = 0.588$) or the post-imaging questionnaire (Spearman’s $\rho = −0.011$, $P = 0.971$).

The percentage of consistent responses between the choices made during the imaging task and for the post-imaging questionnaire was compared with the participant’s IQ score. A significant correlation was found between consistency and IQ, whereby the

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**Table 2** Percentage of consistent choices made by the PWS participants across measures

<table>
<thead>
<tr>
<th></th>
<th>Imaging task vs. post-imaging questionnaire</th>
<th>Interview vs. imaging task</th>
<th>Interview vs. post-imaging questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Consistent choices</td>
<td>69.60</td>
<td>90.93</td>
<td>90.28</td>
</tr>
<tr>
<td>SE</td>
<td>2.53</td>
<td>1.42</td>
<td>1.56</td>
</tr>
</tbody>
</table>

higher the IQ of the participant, the greater number of consistent responses were made (Spearman’s Rho = 0.675, P = 0.016).

Pattern of food preferences
Preferences according to the main macronutrient content of food

For the comparison group, there was a significant difference between mean ranking given to the three food types \(Z = 6.681, P = 0.035\) (Fig. 1a). Post hoc comparisons showed that high protein foods were significantly more preferred than high carbohydrate foods \(Z = -2.672, P = 0.008\) and high fat foods \(Z = -2.576, P = 0.010\). For the PWS group, however, there was no significant difference in the mean ranking of each food type according to the main macronutrient content \(\chi^2 = 5.561, P = 0.062\) (Fig. 1a). When the preferences of the two groups were compared, the PWS group showed a significantly greater preference for high carbohydrate foods than did the non-PWS group \(\chi^2 = 3.945, P = 0.047\), whereas no significant difference was found in the ranking of high protein foods \(\chi^2 = 0.189, P = 0.664\) or high fat foods \(\chi^2 = 1.210, P = 0.271\).

Preferences according to the taste of food

For the comparison group, no significant difference was found in the mean ranking for the different taste categories \(\chi^2 = 1.226, P = 0.747\) (Fig. 1b). For PWS group, however, there was a significant difference in the ranking across the taste categories \(\chi^2 = 17.946, P < 0.0001\) (Fig. 1b). Post hoc comparisons of the food types showed that sweet foods were significantly more preferred than salty foods \(Z = -2.408, P = 0.016\), bland foods \(Z = -2.748, P = 0.006\) and sour foods \(Z = -3.322, P = 0.001\). Salty foods were significantly more preferred over sour foods \(Z = -2.156, P = 0.031\) but not bland foods \(Z = -1.493, P = 0.135\). A significantly different preference for sweet foods was found between groups, whereby the PWS group ranked sweet foods higher than the non-PWS group \(\chi^2 = 4.142, P = 0.042\).

Incentive ratings

As expected, a significant difference was found between the incentive ratings from the post-imaging questionnaire of foods in the high and low conditions for those with PWS \(Z = -3.048, P = 0.002\). Foods presented in the high incentive condition were, on average, given a higher incentive rating (mean = 4.53; SE = 0.09) than the foods in the low incentive condition (mean = 4.08; SE = 0.13). The mean rating for the high and low condition for each participant is shown in Fig. 2. This shows that the majority of ratings were high, indicating that the participants would like to eat the majority of the foods.

Neuroimaging

To investigate the rCBF changes associated with incentive, all of the 12 scans from the three imaging sessions were compared directly, regardless of prior fasting or food intake. When activity associated with
the high incentive condition was compared with the low incentive condition (High–Low contrast), no significant differences were observed for a particular macronutrient (protein, carbohydrate or fat) in those with PWS. The lack of a strong preference for a particular macronutrient (protein, carbohydrate or fat) in those with PWS supports the findings from a previous study (Joseph et al. 2002), although those with PWS in this study did prefer high carbohydrate foods more than those without, in line with the findings of Fieldstone et al. (1997). As the preference for carbohydrates was not significantly greater than other types of food, this result does not support the idea put forward in the introduction that abnormalities in the neurobiology of the hypothalamus, for example, underlie food preferences in PWS. As in those without PWS, other brain regions, such as the ventral striatum, may mediate preference for and liking of foods (Kelley et al. 2002; Berthoud 2004). It should be noted that participants were not instructed to consider the foods in terms of the intended macronutrient or taste category, so it is possible that their preferences were based on different aspects of the foods.

A significantly greater preference for sweet-tasting foods, over salty, bland and sour foods, was found in the PWS group compared with the non-PWS group. Previously, it has been found that individuals with PWS could not reliably discriminate between sweet foods containing sugar or aspartame, suggesting that it is the sweet taste that they prefer over the post-ingestive effects of consuming the food (Taylor &
Caldwell 1985). Individuals without PWS, however, have also shown a preference for sweet foods (Glover et al. 1996; Rankin & Mattes 1996), suggesting that a preference for sweet foods in those with the syndrome may not be abnormal. The strength of the preference, however, may be dysfunctional. Sweet-tasting foods are likely to contain high levels of sugars and so could contribute to weight gain.

As the above discussion highlights, individuals with PWS do have food preferences; therefore, it could be expected that the incentive to eat different foods would vary according to those preferences. In two groups of people without PWS, imagining a prospective meal composed of highly valued foods produced activation in the vicinity of the amygdala and a region of the left medial OFC (Arana et al. 2003; Hinton et al. 2004). However, using a similar task where individuals with PWS considered photographs of foods and imagined what they would like to eat, greater activation in the amygdala or medial OFC was not found to be associated with the highly valued foods (i.e. the High–Low contrast), even after those were excluded who did not rate food items differently in the two conditions. Nonetheless, foods in the ‘high incentive’ condition were, on average, given a higher incentive value than the foods in the ‘low incentive’ condition as intended. Moreover, there was no significant interaction between the incentive value of the foods presented, as described in this paper, and the level of fasting or food intake of the participants before the imaging sessions (fasting, 400 kcal and 1200 kcal conditions). This is in contrast to the findings of a non-PWS study in which a region of the lateral OFC was activated during hunger relative to satiety only when high incentive food items were considered (Hinton et al. 2004).

The lack of significant activity in the amygdala and medial OFC in association with the high incentive foods for this PWS group compared with the non-PWS group is unlikely to be due to a difference in power, given the greater number of participants in the PWS group and the specific brain regions of interest. It is possible that the adaptations to the imaging task made for the PWS study may not have led to the same incentive responses as the task given to those without PWS; however, the instructions and design of the task were kept as similar as possible, and additional practice trials increased the likelihood that the task would be completed as intended. Therefore, it is probable that while there was a difference between the incentive value of foods in the high and low incentive conditions for those with PWS, this may not have been sufficiently great to be associated with differential brain activity in the amygdala and medial OFC. This may be explained by the impact of the dysfunctional satiety system on incentive processes.

This finding also raises the possibility that the processes underlying incentive may be dissociable from the processes underlying food preference in PWS, as the latter process appears largely preserved, whereas it appears that incentive motivation in those with PWS may in some way be affected by the consequences of their genetic abnormality on feeding and reward pathways. This could be a result of dysfunctional brain activity in, or connections with, the hypothalamus, their appetitive behavioural problems or because of their learning disability. This suggestion does support evidence that the brain substrates of liking and wanting are dissociable (e.g. Berridge 1996). Relative liking of different foods may not be influenced by dysfunctional satiety processes, but such processes may lead to a greater incentive to eat all foods, in order to increase feelings of fullness, thereby reducing the subsequent contrast between the ‘high incentive’ and ‘low incentive’ conditions. Indeed, those with PWS in this study gave the items in the ‘low incentive’ condition significantly higher incentive ratings than did the group without PWS in the previous study (Hinton et al. 2004).

Issues have previously been raised about the suitability of the assumptions and statistical analyses of neuroimaging designs to the study of developmental disorders (Johnson et al. 2002). Brain images from participants are warped into the shape of a standard brain so that data from individuals can be grouped for the analysis and that data can be compared from separate studies. This process of normalization requires that the structures of the brains in the analysis are not significantly different. As PWS is associated with mild to moderate learning disability, resulting in a mean IQ of the participants of 70.5, differences in brain functions and structures at a neuronal level are possible. However, few gross morphological differences have been found (e.g. Cacciari et al. 1990; Hayashi et al. 1992; Leonard et al. 1993; Hashimoto et al. 1998), so this normalization process was deemed appropriate for this group.
In conclusion, using neuroimaging, we can now suggest that the dysfunction in the neural satiety system of those with PWS (Hinton et al. 2005; Shapira et al. 2005) overpowers the input from the incentive reward pathways, so that activity in those pathways cannot guide behaviour towards the consumption of high preference foods. Therefore, although those with PWS have food preferences, they do not always behave in a manner consistent with those preferences, as their incentive to eat many foods is high. Further understanding of the neuropsychological and neuronal satiety system in PWS is necessary to explain how this system impacts on the usually powerful influence of the reward pathways, and may prove important for the design of future treatment programmes and research into the eating problems of those with PWS.

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