

## Etiology and Pathophysiology/Diagnostics

# Neuroimaging and obesity: current knowledge and future directions

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### Summary

Neuroimaging is becoming increasingly common in obesity research as investigators try to understand the neurological underpinnings of appetite and body weight in humans. Positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetic resonance imaging (MRI) studies examining responses to food intake and food cues, dopamine function and brain volume in lean vs. obese individuals are now beginning to coalesce in identifying irregularities in a range of regions implicated in reward (e.g. striatum, orbitofrontal cortex, insula), emotion and memory (e.g. amygdala, hippocampus), homeostatic regulation of intake (e.g. hypothalamus), sensory and motor processing (e.g. insula, precentral gyrus), and cognitive control and attention (e.g. prefrontal cortex, cingulate). Studies of weight change in children and adolescents, and those at high genetic risk for obesity, promise to illuminate causal processes. Studies examining specific eating behaviours (e.g. external eating, emotional eating, dietary restraint) are teaching us about the distinct neural networks that drive components of appetite, and contribute to the phenotype of body weight. Finally, innovative investigations of appetite-related hormones, including studies of abnormalities (e.g. leptin deficiency) and interventions (e.g. leptin replacement, bariatric surgery), are shedding light on the interactive relationship between gut and brain. The dynamic distributed vulnerability model of eating behaviour in obesity that we propose has scientific and practical implications.

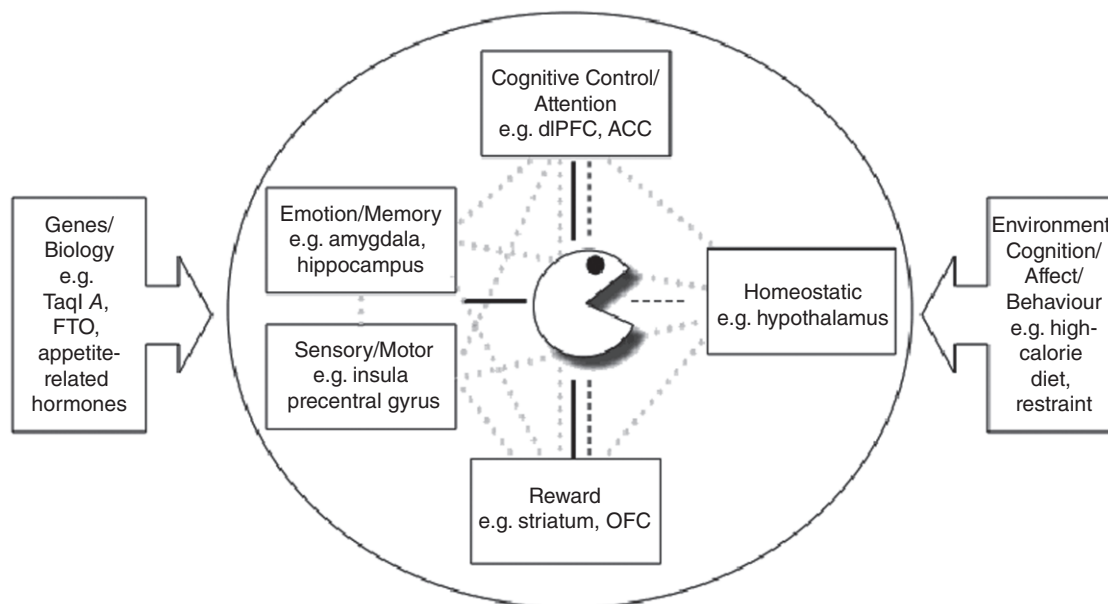
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### Introduction

The obesity epidemic is undoubtedly related to the multiple 'obesogenic' influences in modern society. But despite the pervasiveness of fast food restaurants and large portion sizes, not everyone becomes obese, suggesting that individuals differ in their susceptibility to environmental opportunities to eat (1). Neuroimaging studies using positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetic resonance imaging (MRI) are beginning to yield valuable insights into the neurobiology underlying variation in eating behaviour in humans. However, making sense of the rapidly accumulat-

ing work in this area is challenging, and existing reviews – while excellent and useful – focus on gut hormone studies (2), commonalities between addiction and eating behaviour (3), or pleasure and hedonic processing as exemplified by eating (4). Although obesity has much in common with other disorders of hedonic excess (e.g. drug addiction), eating behaviour is distinctly complex in that we require food to live and have consequently evolved elaborate homeostatic and other mechanisms to insure intake. In addition, food-related environmental factors (e.g. diet, social influences) begin to influence our biology, and our perceptions, memories, cognitions, emotions and behaviours, in early life. Our internal representations of eating



**Figure 1** Dynamic distributed neurobehavioural vulnerability model of eating behaviour in obesity.

Bold lines represent exaggerated appetite-related signals, broken lines represent impaired appetite-related signals, and grey dotted lines represent functional interactions between brain areas. For example, satiety signalling from homeostatic areas seems to be impaired (e.g. delayed fMRI inhibition response in hypothalamus) while hunger signals from emotion/memory areas and sensory/motor areas seem to be heightened (e.g. greater activation in amygdala, hippocampus, insula and precentral gyrus in response to food cues), in obese individuals. The functioning of the neurobehavioural system depends on genetic, biological and environmental influences, as well as cognitions, emotions and persistent patterns of behaviour (as well as interactions between these factors). To take a specific example, the role of reward areas may depend on dietary behaviour and genetic factors. For example, long-term exposure to highly palatable high-calorie foods may lead to *decreased* reward activation following food intake, but *increased* reward activation following food cues, in obese individuals. Alternatively, individuals with a genetic reward deficit may show *decreased* reward activation to both intake and cues. Both routes may cause individuals to compensate by over-eating. There is also evidence that the recruitment of cognitive control areas varies between obese individuals, depending on their habitual level of cognitive and/or behavioural dietary restraint. The areas included in this diagram are distributed all over the brain and interact with each other (i.e. functional connectivity), producing the complex and variegated phenotypes associated with common, multifactorial forms of obesity.

behaviour may therefore be richer than for behaviours that are later acquired, less rehearsed and not so inextricably woven into the fabric of everyday life.

The purpose of this paper is therefore to take a more comprehensive approach to the literature. Our primary goals are to provide a detailed discussion of the methods and findings of all studies falling under the umbrella of neuroimaging research of eating behaviour relating to obesity, and to propose a broad, dynamic, distributed neurobehavioural vulnerability model to account for existing findings (see Fig. 1). In the simplest version of this model, *hyper*-activity relating to food in brain areas associated with reward, emotion/memory and sensory/motor processing, paired with *hypo*-activity relating to food in areas associated with homeostatic satiety and cognitive control/attention, result in an eating behaviour phenotype that leads to over-eating and obesity. This obesogenic pattern of brain activity is influenced by genetic, biological and environmental factors, as well as cognitions, emotions and persistent patterns of behaviour (as well as interactions between these variables), and is therefore trait like to some

degree, but can also change, and is amenable to intervention. For example, excessive long-term exposure to highly palatable high-calorie foods may cause *decreased* reward area activation following intake in obese groups, while consistent attempts at dietary restraint may be associated with *increased* activation in cognitive control areas in response to food cues or intake, even if the attempts are ultimately unsuccessful. An individual's unique pattern of brain responses to food and food-related stimuli may help to explain his or her appetitive behaviours.

Since our intention is to provide a useful resource for research scientists, we have organized our review by the dominant design of each study, hoping this will enable readers to evaluate the extent to which each study answers its intended question, and to identify where research gaps remain and how existing studies could be replicated and/or improved on. To facilitate interpretation of the rather complex findings, we summarize how the results fit with our distributed vulnerability model at the end of each section. We also include some of the known functions subserved by each brain area in parentheses where it is first

mentioned – although it should be noted that these notes, and our interpretations of the results, are simplified and not exhaustive. For example, ‘memory’ does not constitute a complete description of hippocampal function, and the brain’s capacity for memory involves many more structures than the hippocampus alone. However, hippocampal activation is likely to indicate memory formation or retrieval and we believe that highlighting this possibility gives a useful starting point for interpretation and hypothesis generation.

## Overview of methodology

The aim of most neuroimaging methods is to assess brain activity relating to cognition, affect and behaviour. PET and fMRI are used most frequently in obesity research. PET provides topographic information about brain activity by detecting gamma photons emitted from decay particles (positrons) of a radioactive tracer (e.g. fluorodeoxyglucose), which is introduced into the bloodstream and taken up by biologically active molecules (e.g. glucose). Dopamine levels may also be inferred from PET by injecting radioligands (e.g. [<sup>11</sup>C] raclopride), which compete with endogenous dopamine at certain receptor sites (e.g. D2/D3). In contrast, fMRI infers local neuronal activity from blood-oxygen-level dependent changes in the paramagnetic properties of haemoglobin. Structural MRI may also be used to obtain anatomical detail, based on the differing paramagnetic properties of brain tissues including grey and white matter.

A common paradigm in fMRI studies is to examine the brain’s response to visual, olfactory or gustatory (taste) food vs. control cues, or to different categories of food cue (e.g. high vs. low palatability, high vs. low calorie). Stimuli are often presented in a *block* design, i.e. subjects are shown multiple stimuli of one category in one run, then multiple stimuli of another category in a separate run, allowing accumulation of hemodynamic responses. *Event-related* designs, in which stimuli are presented in a mixed, pseudo-random order allowing discernment of unique responses to single stimuli, are also growing in popularity (5). Other studies assess resting brain activity before and after ingestion of a substantial caloric load.

In addition to these variations in design, studies differ in subject characteristics (e.g. age, sex, dieting status, eating behaviour) and other important features (e.g. length of fast prior to scan). There is also diversity in image acquisition and analysis. For example, some enhance image quality in small regions of special interest (e.g. hypothalamus) by narrowing the field of view to that area and acquiring thinner ‘slices’ to improve spatial resolution. In addition, while it is common to take an exploratory ‘whole-brain’ approach to analysis, studies are increasingly using masking to maximize statistical power to detect activation differences in a hypothesis-driven set of ‘regions of interest’

(ROI) selected on the basis of previous literature. These differences may help explain disparities in results, and are therefore highlighted throughout.

## Studies comparing lean and obese adults

An informative approach in neuroimaging and obesity research is to compare patterns of brain activation in obese (body mass index [BMI] > 30) and lean (BMI < 25) individuals, who are matched for other salient characteristics, such as age and gender. Some studies including both lean and obese individuals have also reported relationships between brain activation and BMI.

### Visual stimuli

Examining differences in neural responses to food pictures between obese and lean individuals may help us understand weight-related differences in responses to ‘real-life’ external cues, such as food displays, menus and ads. Using a block design, one fMRI study assessed responses to pictures of high-calorie foods (e.g. hamburgers), low-calorie foods (e.g. vegetables), eating-related utensils (e.g. spoons) and neutral images (e.g. waterfalls, fields), following abstinence from eating for at least 1.5 h. Obese (BMI > 31) vs. lean (BMI 19–24) women showed greater activation to high-calorie foods vs. neutral images in the caudate/putamen (reward/motivation), anterior insula (taste, interception, emotion), hippocampus (memory) and parietal cortex (spatial attention) (6).

In a similar study, following an 8–9 h fast, obese (BMI 31–41) vs. lean (BMI 20–25) women showed greater activation in the nucleus accumbens (NAc)/ventral striatum (reward/motivation) and caudate/putamen, medial and lateral orbitofrontal cortex (OFC; reward, emotional decision-making), insula, amygdala (emotion), hippocampus and also in the medial prefrontal cortex (mPFC; motivation, executive function) and anterior cingulate cortex (ACC; conflict monitoring/error detection, cognitive inhibition, reward-based learning), in response to pictures of high-calorie foods (e.g. cheesecake) vs. non-foods (cars), as well as greater activation to high- vs. low-calorie food pictures (e.g. broiled fish) in similar regions (7). Functional connectivity analyses, which assess the co-activation of spatially remote brain areas, additionally revealed a relative deficiency in the amygdala’s modulation of OFC and NAc activity, paired with excessive modulation of the NAc by the OFC, in the obese (8).

More recently, a study measuring both preprandial (after 4 h fast) and postprandial (after 500 kcal standardized mixed meal) activation in response to pictures of high- and low-calorie foods (e.g. vegetables, desserts) vs. non-foods (animals) in obese (BMI 30–38) vs. lean (BMI 20–25) men as well as women in a number of regions of interest

revealed greater pre-meal activation in the ACC and mPFC and greater post-meal activation in the caudate, hippocampus, mPFC and superior frontal gyrus (self-awareness) among the obese (9).

Together, these studies suggest that obesity is consistently associated with heightened or abnormal responses to visual food cues in a distributed network of brain regions involved in reward/motivation and emotion/memory. There is also some evidence for heightened activation in areas associated with cognitive control/attention, which may be more pronounced in the fasted state. Although it is not possible to infer cognitive functions from brain activation, this could reflect individuals associating the cues with cognitive efforts to restrain intake.

### Gustatory/olfactory cues

Brain responses to the taste and smell of food also seem to differ between obese and lean adults. In one of a series of innovative PET studies, Del Parigi *et al.* (10) found that obese (BMI > 35) vs. lean (BMI < 25) individuals showed greater activation in the midbrain (reward) and middle-dorsal insula, and lesser activation in the posterior cingulate cortex (PCC) (awareness, attention), temporal cortex (object processing, memory) and OFC, in response to a 2 mL taste of a liquid meal vs. baseline following a 36 h fast. Further, in an fMRI study, obese vs. lean persons showed greater responses to odours of sweet and fat-related foods (e.g. chocolate cake, roast beef) vs. non-foods (e.g. grass) in the hippocampus/parahippocampal gyrus following a 24 h fast (11).

Combined, these results suggest that food tastes and even food odours are capable of triggering heightened responses in key reward/motivation and emotion/memory areas in obese individuals, potentially promoting intake. Conversely, obese individuals may show less activation in areas associated with attention and object processing, potentially reflecting a relative absence of objective evaluation of stimuli, which could be caused by or related to a relatively stronger hedonic (reward) response.

### Food ingestion

Other studies have examined responses to the ingestion of more substantial amounts of food, producing mixed findings. For example, in one fMRI study, a midsagittal slice of the hypothalamus – essential for the homeostatic regulation of intake but difficult to detect in whole-brain analyses due to its small volume – was continuously imaged for 50 min before, during and after ingestion of an oral glucose load (75 g) following a 12 h fast. Results revealed that whereas lean men demonstrated an *inhibitory response* (i.e. decreased activation over time) in the hypothalamus, obese men failed to show this pattern (12).

Extending these results, a PET study showed *attenuated decreases* in not only hypothalamic, but also thalamic and limbic/paralimbic activity in obese (BMI  $\geq$  35) vs. lean (BMI  $\leq$  25) men (13). This study also reported *greater* activation in the ventromedial, dorsomedial, anterior lateral and dorsolateral PFC (dlPFC; cognitive control) after a nutritionally complete (50% daily Resting Energy Expenditure [REE]) liquid meal administered directly following a 36 h fast (13). However, a later study using a more sensitive method to analyze the same data, as well as additional data from a new sample of men consuming a fixed amount (400 kcal) liquid meal, failed to replicate many of these findings. The only consistent result was that obese (BMI  $\geq$  35) vs. lean (BMI  $\leq$  25) adults showed *less* post-prandial activation in the dlPFC (14). This result has also been found in comparisons of obese vs. lean women (15).

Consistent with the distributed nature of our model, the results suggest that over-eating in obese individuals may be related to a combination of sluggish homeostatic responses to satiety in the hypothalamus, and a reduced inhibitory response in the dlPFC.

### Dopamine function

The role of dopamine in reward and motivation makes it highly relevant to the motivated behaviour of eating. A number of studies have now shown that overweight (BMI  $\geq$  25) vs. lean (BMI < 25) people have a higher prevalence of the TaqI A1 allele of the dopamine D<sub>2</sub> receptor (DRD2) gene, which is associated with low D<sub>2</sub> receptor availability (16–18). PET data have also revealed lower striatal D<sub>2</sub> receptor availability in obese vs. lean men both at rest and following IV glucose (19,20). Further, a study of very obese (BMI > 40) vs. non-obese (mean BMI 25) men and women found an association between decreased receptor availability and decreased activation in dlPFC and ACC, as well as in OFC and somatosensory cortex (food reward), in the obese group (21).

On the whole, these results support a pattern of systemic ‘hypo-responsivity’ in reward centres that co-exists with the food cue-specific ‘hyper-responsivity’ observed in the visual/taste cue studies. As suggested earlier, and reflected in the dynamic component of our model, this may occur because with repeated exposure to high-calorie foods – perhaps partially triggered by an initial hyper-responsivity to food cues – dopamine receptors become down-regulated (22). This down-regulation may then counter-intuitively *enhance* responsiveness to cues signalling high- vs. low-palatability foods, since they promise a ‘hit’ that is big enough to overcome the blunted reward response (23). A similarly paradoxical pairing of increased ‘wanting’ (i.e. cue-triggered motivation to eat) and decreased ‘liking’ (i.e. actual enjoyment of eating) (24) is evident in addiction (25).

## Structural differences

Studies are also beginning to link obesity to structural differences within the brain. For example, MRI scans of two samples of healthy adults (40–66 years and 17–79 years, respectively) demonstrated a linear association between higher BMI and smaller brain volume (26), particularly within the grey matter (27). Another study including obese ( $32 \pm 8$  years), and lean ( $33 \pm 9$  years) individuals localized these grey matter density differences to the putamen, frontal operculum and post-central gyrus (taste, interception), and middle frontal gyrus (executive control) (28). A separate study of cognitively normal elderly subjects who were obese ( $77 \pm 3$  years), overweight ( $77 \pm 3$  years) and lean ( $76 \pm 4$  years) reported reduced volume in the thalamus (sensory relay, motor regulation), hippocampus, ACC and frontal cortex (29).

So far, these reports have been based on cross-sectional data in adults, so we do not know whether the deficits precede or follow obesity. However, the volume reductions in areas associated with reward and control could be corollaries of the functional activation deficits observed in these areas, and may help explain the over-eating phenotype of obesity. Reduced volume in structures such as the hippocampus may also help to explain the higher rates of dementia (30,31) and cognitive decline (32) in obese people. Biological mediators could include the physiological effects of sleep apnoea (33), increased adipose tissue hormone secretions such as leptin (34), or release of pro-inflammatory factors caused by consuming high-fat diets (35).

## Studies of weight change

Comparing currently obese and lean people gives us useful information about the neurobiology of obesity, but does not allow us to infer whether neurological abnormalities precede, follow or simply accompany the obese state. Examining relationships between brain activation and weight change may help illuminate temporal order, and therefore causal mechanisms. Although the gold standard for testing effects of weight change is a prospective design, cross-sectional studies comparing formerly obese (post-obese) individuals with currently obese or lean individuals have also been informative because abnormalities in this group are not confounded by current obesity, and may therefore reflect predisposing neurobehavioural risk factors for obesity, or at least risk factors for weight regain.

## Cross-sectional studies

One of the first studies of post-obese (i.e. weight reduced from BMI 35 to 25 and stable for at least 3 months)

individuals focused on PET activation after a 2 mL taste of liquid meal following a 36 h fast. Results revealed increased insula activation in obese and post-obese, compared with always-lean, persons (36). Another study showed that while overfeeding (30% above eucaloric needs for 2 d) produced an *attenuation* of insula, hypothalamus and visual cortex responses in response to images of palatable food vs. non-food among thin (BMI 19–23) individuals, post-obese (8% weight loss) persons failed to show such a pattern (37).

Consistent with our distributed model of vulnerability, these results suggest that individuals with a history of obesity show heightened responses to ingestion in areas associated with taste reward (i.e. insula). These exaggerated responses are evident not only in conditions of assumed hunger (following 36 h fast), but also in conditions of presumed satiety (following overfeeding), and may drive over-eating. Post-obese persons also seem to fail to adapt to overfeeding by down-regulating responses to food cues in homeostatic and sensory areas (i.e. hypothalamus, visual cortex); this unbridled responsivity could contribute to excessive intake.

However, formerly obese persons may not be entirely identical to obese individuals in their neural responses. In support of the dynamic nature of our model, other studies have observed greater activity in the dlPFC after a satiating liquid meal (50% daily REE) not only in lean (vs. obese) women, but also in post-obese (vs. obese) women (14,15). This suggests that while successful dieters may still exhibit heightened appetitive responses to food cues and blunted inhibitory responses to excessive intake, they are able to compensate for this by engaging control regions in the brain in a similar manner to those who remain consistently lean.

## Longitudinal studies

An advantage of longitudinal studies of weight change is that the within-subjects design affords greater power, and prospective studies are less vulnerable to selection artefacts. This is important because the post-obese people in the cross-sectional studies cited above had achieved enduring weight loss and may not, therefore, be representative of a normal high-risk population. Since weight loss was achieved by a variety of different routes, there may also have been significant variability in the post-obese phenotype.

Using a prospective design, Rosenbaum *et al.* (38) studied six obese individuals who achieved 10% weight loss on a standardized inpatient 36–62 d liquid formula diet. Post intervention, when they switched to a weight-maintaining formula diet, visual presentation of actual foods (e.g. fruits, grains, sweets) vs. size-matched non-foods (e.g. cellphone, jump rope) following an overnight

fast elicited *greater* fMRI activation in the ventral pallidum (reward-based action), brainstem (sensory and motor relay), parahippocampal gyrus, cerebellum (motor learning, emotion), middle temporal gyrus (visual and semantic processing) and inferior frontal gyrus (cognitive inhibition), as well as *lesser* activation in the amygdala, hippocampus, precentral gyrus (motor planning), inferior parietal lobule (sensory integration, visuospatial processing, attention), cingulate and middle frontal gyrus (executive function).

These results suggest a complex pattern of changes that may reflect a diet-induced conflict between approach and avoidance responses to food and could have the net effect of promoting intake to defend the obese state, at least in the short term. For example, the increased reward area activation post-diet could reflect a temporary up-regulation in reward responsivity (likely to promote excessive intake), while the decreased amygdala and hippocampus activation could reflect decreased emotional and memory-related responses, which could potentially promote abstinence from excessive eating. These distributed effects could be attributable to the monotony of the liquid diet, the decreased energy intake or both, and emphasize the impact of environmental/behavioural variables such as dieting on neurobehavioural vulnerability to obesogenic eating patterns.

An alternative method is to examine the effects of weight *gain* in free-living subjects. In a study of overweight and obese young women, subjects who showed a >2.5% increase in BMI over a 6-month follow-up period (mean BMI change, 4.4%, mean weight change, 2.9 kg) vs. subjects who were weight stable (<2% change in BMI, mean BMI change 0.05%, mean weight change 0.2 kg) showed significantly less activation in an ROI analysis of the caudate in response to intake of 0.5 mL of chocolate milkshake (39).

The weight gain in this study was modest, and it is unclear whether the results would generalize to subjects not yet overweight. However, they provide some support for a dynamic vulnerability interpretation, in which weight gain and increased food intake lead to hypo-responsivity to food ingestion in reward-related brain regions (22).

### Studies of children and adolescents

Since brain structure and function change throughout development – particularly within frontal regions – results in adults may not generalize to younger people. It is therefore essential to conduct separate studies in children and adolescents. These studies may also reveal potential predictors of weight gain, since early-appearing irregularities are less likely the result of the metabolic and behavioural consequences of long-term obesity.

### Visual stimuli

In the only currently published study to include pre-teens as well as teens with common forms of obesity (i.e. no known single gene mutations), obese vs. lean 10–17-year-old boys and girls showed greater preprandial (after 4 h fast) activation in the PFC and greater postprandial (after 500 kcal standardized mixed meal) activation in the OFC in response to pictures of high- and low-calorie foods (e.g. vegetables, desserts) vs. non-foods (animals). The obese group also showed relatively smaller post-meal (vs. pre-meal) decreases in NAc, limbic and prefrontal activation to food pictures vs. control (blurred image) stimuli (40). Data from other groups are somewhat consistent. For example, one study of adolescent girls (mean age 15.5; BMI 17–39) found that higher BMI was associated with *greater* putamen, OFC and frontal operculum activation in response to pictures of processed foods, fruits and vegetables they had rated as *appetizing* vs. pictures of foods they had rated as *unappetizing*, or glasses of water, following a 4–6 h fast (41).

### Food ingestion

In a study of adolescents, fMRI responses were assessed not only to visual stimuli – in this case, conditioned cues (i.e. three shapes associated with delivery of chocolate milkshake, tasteless solution or nothing) – but also to 0.5 mL tastes of the milkshake. Obese vs. lean girls showed greater activation in the anterior and middle insula and somatosensory region in both conditions, but decreased caudate activation in the taste condition (23). This blunted striatal response to intake has now been demonstrated in three different samples by the same research group (23,42).

The visual stimuli and food ingestion results suggest that, like obese adults, obese children experience *greater* reward area responses to visual food cues in parallel with *lesser* responses to food ingestion, with both potentially maintaining over-eating. It is unclear how the greater pre-meal activation and more persistent post-meal activation of the PFC in Bruce *et al.* (40) should be interpreted, but – consistent with the interactions between brain areas and impact of cognitive/behavioural factors represented in our broad model – the authors suggest it may reflect attempts to inhibit appetitive responses in the context of increased food motivation. Since these participants presumably developed obesity relatively recently, it is possible that the response combination was predictive of obesity – but given that they were already obese, temporal relationships cannot be inferred.

### Studies of samples with high genetic risk

Greater insight into causal mechanisms may be gained by examining those who are not yet obese but are at high risk

for obesity due to genetic factors, since abnormalities may constitute risk factors for weight gain. Tracking future weight change additionally allows assessment of the predictive power of these factors.

### Candidate genes

Stice *et al.* have related fMRI responses to food stimuli to genes associated with dopamine function. For example, neural activation in response to tastes of a milkshake vs. a tasteless solution was assessed in female college students (18–22 years, BMI 24–33) and adolescent girls (14–18 years, BMI 18–39) following a 4–6 h fast. Higher BMI was found to be associated with *lesser* caudate activation, particularly in those with the DRD2 TaqI A1 vs. A2 allele (42). A later study of adolescent girls' (BMI 17–39) responses to food pictures following a 4–6 h fast found that higher BMI was associated with *greater* putamen, OFC and frontal operculum activation in response to pictures of appetizing foods vs. unappetizing foods or glasses of water. However, for those with the TaqI A1 allele or the DRD4-7repeat allele, the relationship was weaker, and *lesser* activation in the specified brain areas predicted greater weight gain 1 year later (41).

These results suggest that genetically influenced hypo-responsivity in taste reward areas to food – and possibly also to food cues – may place at least a subgroup of individuals at risk of weight gain. Specifically, A1 allele status may enhance risk of excessive eating and weight gain via an innately blunted striatal responsivity to both food and food cues, which leads individuals to seek out large quantities of highly palatable foods to achieve a reward response. In contrast, the majority of obese people, who do not exhibit this genetic risk profile, instead follow the dynamic pattern outlined earlier, in which initial hyper-responsivity to food leads to over-eating, subsequent down-regulation of reward responses to ingestion, and maintained hyper-responsivity to food cues. The genetic risk examined here may therefore promote initiation and maintenance of over-eating and obesity within certain individuals, but is unlikely to provide a general explanation for common obesity.

### Common obesity genes

No studies have yet reported associations between brain function and the recent crop of genes associated with common obesity that have been discovered via genome-wide association studies (GWAS) (43). However, a recent study of healthy elderly (mean age  $76 \pm 5$  years) subjects found that carriers of the C allele at rs1421085 and the G allele at rs17817449 on fat mass and obesity-associated protein (FTO) (highly expressed in the brain, and the first common gene to be associated with obesity) had an 8% volume deficit in the bilateral frontal lobe, and a 12% deficit in the bilateral occipital lobe (44).

Further research is necessary to elucidate mechanisms and whether the results are independent of current body weight. However, the volume deficit in the frontal lobe (important for executive function and inhibitory control) may be consistent with the evidence presented earlier for lesser postprandial activation in the prefrontal cortex among obese persons. A significant challenge is the small effect size of currently known gene variants: the 32 common variants currently identified via GWAS as being associated with BMI explain only 3% of variance in weight and have limited predictive power (45). Future research may benefit from using fMRI paradigms that specifically tap aspects of the obese phenotype known to be associated with certain gene variants (e.g. specific eating behaviours) (46,47).

### Parental obesity

Clues to the neurobiology of genetic risk may also be gained by studying individuals at high or low risk based on parental obesity status – although this of course is a marker of environmental as well as genetic risk. In a study of currently lean male and female adolescents, those with two obese parents vs. two lean parents showed greater activation in the caudate, frontal operculum and parietal operculum (secondary somatosensory cortex) in response to tastes of chocolate milkshake (48).

This finding requires replication but is consistent with a dynamic model of reward responsivity such that high-risk children initially display a heightened responsivity to milkshake ingestion in taste reward areas. This heightened responsivity motivates repeated intake of high-calorie foods, which in turn leads to the reduced reward responsivity (but maintained over-eating) that is exhibited by obese adults.

### Studies of specific eating behaviours

A disadvantage of focusing on the broad biological phenotype of BMI is that it ignores the fact that body weight is likely to be the cumulative result of a range of specific eating behaviour traits (49). Examining the neural correlates of these 'endophenotypes' may enrich our understanding of the biobehavioural mechanisms of appetite, as well as help to explain some of the inconsistencies in obese vs. lean comparison studies.

### External eating

The extent to which cues such as the sight of appetizing foods evoke desire to eat – often in the absence of physiological hunger – has been termed 'external eating' and is higher in heavier individuals. In a study of lean adults, 'external food cue sensitivity' scores were calculated from self-report questionnaires, and participants were presented

with food pictures following a 2 h fast. Higher questionnaire scores were associated with *greater* functional connectivity between the ventral striatum and emotion/motor preparation structures (amygdala, premotor cortex), and *lesser* connectivity between the ventral striatum and amygdala and attention-related regions (dorsal ACC, ventral ACC), in response to appetizing vs. bland pictures (50).

The limited temporal resolution of fMRI does not permit determination of the direction of information flow. However, based on known anatomical connections, the authors propose that external eating is associated with greater modulation of the ventral striatum by the amygdala, greater transformation of striatally mediated desire to eat into motor plans (premotor cortex) and inadequate modulation of ventral striatum and amygdala activity by the ACC. The results support the hypothesis that obesity is associated with dysregulated crosstalk, as well as activation, in a distributed network of areas involved in reward, emotion, motor planning and cognitive control.

### Dietary restraint

A related component of the obese phenotype is dietary restraint. Intuitively, we may think obese people would lack restraint. However, cognitive (if not behavioural) restraint can be high in those who try (successfully or unsuccessfully) to lose weight. Consistent with PET studies of ingestion showing greater dLPFC responses among proven restrainers (post-obese) (14,15), Del Parigi *et al.* (51) reported that higher three factor eating questionnaire restraint scores in women who had successfully reduced their BMI from at least 35 to 25 were associated with *greater* dLPFC responses, and *lesser* OFC responses, to small tastes of liquid meal presented after a 36 h fast. However, consistent with other evidence for enduring responses in food reward areas among successful dieters (36,37), Volkow *et al.* (52) found that higher scores on the Dutch Eating Behavior Questionnaire (DEBQ)\_restraint scale (53) were associated with *greater* increases in dopaminergic activity in the dorsal striatum following presentation of actual foods (selected by the subjects as favourites and warmed to enhance smell), and 0.5 cc tastes of those foods, in lean adults (eight males, two females) who had fasted overnight. Meanwhile, a study of adolescent girls (BMI 17–39) found that restraint scores were positively correlated with activation in the OFC and the dLPFC in response to small tastes of milkshake, while there were no activation differences to food pictures, or cues signalling milkshake delivery (54).

On the whole, the results suggest that cognitive dietary restraint is associated with activation in areas associated with cognitive control (i.e. the dLPFC), and therefore, that the dLPFC activation that has been observed in diverse populations (i.e. lean, obese, post-obese) may reflect the degree to which those participants are engaged in restraint-

related cognitions. The role of reward-associated areas such as the striatum and OFC is less clear but may depend on the extent to which subjects are able to dampen their reward response. For example, the successful dieters in Del Parigi *et al.* (51) may have managed to decrease their OFC response to food cues via long periods of restriction, whereas the adolescent girls (54) and the lean individuals (52) may not have achieved (or even desired to achieve) this goal. In addition, a liquid food consumed after a long fast, as in Del Parigi *et al.* (51), may be less conducive to a reward response than the smell or taste of favoured foods or palatable milkshake (52,54).

### Disinhibited eating

Greater reward responsivity in restrainers may be related to a phenotype that co-occurs with restraint: disinhibition, i.e. the tendency for restraint to break down when confronted by emotional or external cues to eat (55). In Del Parigi *et al.*'s PET study (10), obese adults who showed greater post-fast increases in activation to food tastes in the mid-brain and insula, also reported higher disinhibition. In Martin *et al.*'s fMRI study, obese adults with higher disinhibition showed lesser pre-meal ACC responses to visual food vs. non-food cues while those with higher hunger scores showed greater pre-meal mPFC responses (9). Consistent with a distributed, behaviourally mediated model of obesity vulnerability, these studies suggest that disinhibited eating in obese individuals may be related to the pernicious combination of greater engagement of areas involved in reward/motivation, paired with lesser engagement of those involved in cognitive control.

Disinhibition may also explain the effect of deprivation on fMRI responses to food cues in restrainers: Coletta *et al.* found that when previously fed (500 kcal liquid meal), female restrainers showed *greater* responses to high- (e.g. pizza, cookie) vs. moderate- (e.g. apple, bread) palatability food pictures in areas including the OFC, insula and dLPFC. However, when fasted (8 h), they showed *lesser* activation in the putamen and dLPFC (56). This may reflect that for restrainers, food seems less appetizing when hungry, but more appetizing when full – a pattern placing this population at risk of over-eating after a period of restraint. The impact of this environmental/biological variable (current nutritional status) highlights the dynamic nature of appetitive neural responses and emphasizes the importance of experimental or statistical control of such factors in studies.

### Emotional eating

Many obese people report emotional eating, i.e. consuming (mostly high-calorie) foods in response to emotional states. In Volkow *et al.*'s (52) study of lean adults, DEBQ emotional eating scores were associated with dopaminergic



striatal responses to gustatory and olfactory cues. More recently, a study of adolescent girls (BMI  $24 \pm 5$ ) assessed fMRI responses to receipt and anticipated receipt of a taste of milkshake while in a negative or neutral mood induced by music, following a 4–6 h fast. During the negative vs. neutral state, those in the top quartile on an emotional eating scale showed greater activation in the parahippocampal gyrus and ACC in response to anticipated receipt, and greater activation in the ventral pallidum, thalamus and ACC in response to actual receipt of a milkshake taste. In contrast, those in the lowest quartile showed a reverse pattern of effects (57).

These findings suggest that emotional eating, even among lean individuals, may be associated with heightened reward and emotion area responses to food and food cues, and possibly with enhanced brain activation relating to cognitive control (i.e. ACC). The effect seems to be particularly marked while in a negative mood, highlighting the importance of contextual variables (e.g. current affect), as well as potential variability in neural responses according to behavioural phenotype. The effects of weight, age and gender have yet to be systematically examined.

### Binge eating

Another well-known eating phenotype is binge eating (BE), i.e. excessive intake of food in one sitting combined with a sense of loss of control. BE is sometimes but not always triggered by negative emotions. Using single photon emission computed tomography (SPECT; similar to PET), one study reported increased frontal and prefrontal activation in obese binge eating disorder (BED) (vs. lean non-BED) women after pre-consumption exposure to a freshly cooked meal of their own selection, following an overnight fast (58). A later fMRI study, conducted after consumption of a 650 kcal meal 3 h before scanning, reported greater responses to high-palatability food pictures and auditory food words (desserts, high-fat salty snacks) vs. baseline in the frontal premotor area among obese BE, but not obese non-BE, lean BE or lean non-BE women (59), while another study found that overweight BED women showed greater activation in the medial OFC to high-calorie food pictures, following an overnight fast, than overweight or lean women without BED, and than lean women with bulimia nervosa (60). A more recent study used PET to investigate dopaminergic activity in response to presentations of warmed, subject-selected foods paired with tastes of those foods (via impregnated cotton swabs). Following an overnight fast and oral administration of methylphenidate (a drug that blocks the dopamine transporter and therefore amplifies dopamine signals), obese BED (vs. obese non-BED) individuals showed increased dopaminergic activity in the caudate/putamen in response to food vs. neutral stimulation (i.e. presentation of pictures, toys, clothing items). In addition, higher BE scores

were associated with greater increases in striatal dopaminergic activity in the caudate (61).

Together, these results suggest that BE may be associated with heightened responses to food cues in areas associated with reward, motor planning and attempts at cognitive control. These responses are more pronounced than obese individuals without BE, whose responses are in turn greater than lean individuals. This suggests that BE and obesity are likely to share the same neural substrate, with BE representing a more extreme neurobehavioural phenotype. This phenotype may maintain and exacerbate itself by promoting excessive intake of high-calorie foods, which in turn leads to ingestive reward deficits which fuel further episodes of over-eating.

### Food addiction

The extent to which the compulsive eating seen in obesity is analogous to substance dependence – i.e. typified by tolerance, withdrawal and loss of control – is a subject of ongoing debate. However, a recent study using a questionnaire measure of food addiction found that obese and lean young women enrolled in a healthy weight maintenance programme who had higher food addiction scores showed greater medial OFC, amygdala and ACC responses to anticipated milkshake receipt, and lesser activation in the lateral OFC in response to actual receipt (62).

The results require replication in more generalizable samples. However, the authors point to differentiation of function within the OFC, suggesting that food addiction may be associated with *greater* food cue-related activity in areas involved in subjective evaluation of reward (e.g. medial OFC) and *less* in areas associated with suppression of reward-related responses (e.g. lateral OFC). Interestingly, food addiction was unrelated to BMI here: perhaps those with higher scores were engaging in compensatory behaviours to avoid gaining weight, or high scorers were at risk of weight gain in the future. Either way, the presence of neurobehavioural evidence for obesogenic phenotypes irrespective of obesity suggests that independent study of these phenotypes may allow us to parse out the neurobiology of eating behaviour vs. obesity, and help identify neurobehavioural biomarkers that can predict future weight gain. Notably, food addiction was moderately correlated with DEBQ emotional eating and external eating, highlighting overlap between the phenotypes discussed above. Studies applying the same paradigm across subjects displaying a range of eating behaviours may help to characterize the unique neurobiology of each phenotype.

### Studies of appetite-related hormones

Another promising application of neuroimaging is to investigate neural mechanisms behind established biological

influences on appetite. Certain hormones are known to play a role in the initiation and cessation of eating, and studies examining fMRI responses in individuals with hormone abnormalities, or combining hormone manipulations with neuroimaging paradigms, may help us understand mechanisms of interaction between brain and body in obesity.

### Leptin

Leptin is produced predominantly by fat cells and provides feedback to the hypothalamus regarding fat stores in the periphery. Human and animal studies have advanced understanding of leptin's functions in lean individuals (satiety, lipolysis, suppression of lipogenesis) and its dysfunction in obese individuals, in whom leptin resistance leads to non-suppression of appetite despite high leptin levels. Now, imaging studies are extending existing knowledge of the central pathways involved by demonstrating leptin-associated activation of cortical as well as subcortical brain areas. For example, leptin supplements for leptin-deficient adults have been shown to reduce fMRI activation in the insula, and increase it in the middle, superior and medial frontal gyri, in response to pictures of high-calorie vs. low-calorie foods (63). Similarly, leptin-deficient adolescents who initially demonstrated exaggerated ventral striatum activation in response to food vs. non-food images, whether fed or fasted, showed reductions following 1 week of leptin (64). Leptin supplements may also affect brain responsivity in those without a genetically caused deficiency: obese patients receiving 5 weeks of twice-daily injections of leptin vs. saline after losing 10% of initial weight on a liquid diet showed *less* activation to visual presentation of real foods in the insula, parahippocampal gyrus and middle and superior frontal gyri (38), when in the post-absorptive state.

Further research is necessary to establish the meaning of the observed activation changes. For example, the results suggest that replacing leptin in leptin-deficient or weight-reduced individuals may decrease reward responses to food cues, but it is unclear why frontal responses increased with leptin injections in the leptin-deficient adults (63) yet decreased with leptin supplements in the dieters (38). Nevertheless, these studies suggest that – when functioning normally – leptin acts on a distributed appetitive network in the brain, not only up-regulating homeostatic satiety responses but also possibly down-regulating responses in some taste and reward-related areas (e.g. insula), and thereby acting to maintain energy balance.

### Ghrelin, PYY and GLP-1

A number of hormones produced in the gut also play a significant role in appetite. For example ghrelin, mainly secreted in the stomach, rises before eating and decreases after eating, and is sometimes thought of as an orexigenic

or 'hunger' hormone. Meanwhile, PYY and GLP-1, insulin-promoting hormones secreted in the intestine, rise postprandially and are often thought of as anorexigenic or 'satiety' peptides.

The genetic disorder Prader–Willi syndrome is characterized by a voracious appetite, often leading to morbid obesity. Notably, Prader–Willi individuals display high ghrelin levels and have shown greater postprandial activation to food vs. non-food (animal) pictures in the OFC, insula, hippocampus, parahippocampal gyrus and medial PFC when compared with healthy controls (65). Clues to the contribution of appetite-related hormones to appetite-related brain responses are also provided by bariatric surgery. Roux-en-Y gastric bypass (RYGB), for example, appears to achieve weight loss partly by increasing basal and postprandial PYY and GLP-1. PET findings are mixed: one study found *increased* availability of D2 receptors in the ventral striatum and caudate/putamen (66) 4–6 weeks post-surgery, while the other found *decreased* availability in the same areas as well as the substantia nigra, amygdala, hypothalamus and thalamus, with receptor availability associated with the amount of weight loss at 6–11 weeks (67). We have shown reduced fMRI responses to food cues in ventral tegmental area (VTA), lentiform nucleus (putamen and ventral pallidum), middle frontal gyrus, PCC, culmen (part of cerebellum) and middle temporal gyrus following exposure to pictures and auditory words representing high-ED (vs. low-ED) foods 1 month post-RYGB (68).

Replications and longer follow-ups are required to learn more about the neuroendocrine effects of RYGB. However, the bulk of evidence thus far suggests that heightened responsivity to food cues in reward-related areas (e.g. striatum, VTA, OFC, insula) – as well as other areas – is dampened post-surgery, while impaired responsivity to food ingestion could potentially be corrected. Novel studies combining fMRI with hormone infusions and concurrent hormone measures in obese people also promise to add more detail to the picture; a number of studies of lean persons have already extended animal work to suggest that while ghrelin infusions up-regulate reward area activation, PYY and GLP-1 down-regulate it (69). The results so far support a dynamic model of neurobehavioural vulnerability such that biological interventions that alter gut hormones (e.g. bariatric surgery, novel anti-obesity drugs) may impact appetitive neural systems at various points, influencing eating behaviour and weight.

## Discussion

### Summary

Neuroimaging studies of obese vs. lean individuals are starting to cohere in identifying obesity-related abnormalities in a wide range of brain areas. While most studies

imply a degree of *hyper*-responsivity to food cues such as pictures and smells in reward/motivation areas (in fed and fasted states), there is also growing PET and fMRI evidence for general and intake-related *hypo*-responsivity, particularly in the striatum, a key reward area. Obese individuals also seem to show lesser activation in cognitive control areas such as the dlPFC – as well as reduced brain volume in frontal and other brain areas – and there is some evidence for sluggish responses to food intake in the hypothalamus, a structure implicated in homeostatic regulation of many processes including energy intake. Functional connectivity analyses are also beginning to reveal abnormalities in crosstalk between brain areas.

Further, studies of weight change, obese children and individuals at high genetic obesity risk, are beginning to suggest that abnormal functioning of reward areas – likely influenced by genetics, environmental factors (e.g. long-term intake of highly palatable energy-rich foods) and biological factors (e.g. leptin action) – may help promote weight gain in certain people. However, the study of successful dieters suggests that prefrontal areas associated with cognitive control can counteract these forces to help maintain a healthy weight. Studies of eating behaviours have added further insights, including associations between external eating and abnormal connectivity between reward, motor planning and inhibition areas; between emotional eating and increased food-related activation in areas associated with reward, memory and attention; and between control over eating (higher restraint, lower disinhibition) and dlPFC activation. Finally, studies incorporating hormone measures and manipulations are providing further detail on the interplay between the brain and gut.

Taken together, the results so far support a dynamic, distributed neurobehavioural vulnerability model of eating behaviour in obesity (see Fig. 1). According to this model, satiety signalling from homeostatic areas is compromised while ‘hunger’ signals from emotion/memory areas and sensory/motor areas are heightened. The state of the neurobehavioural system depends on genetic, biological and environmental influences, as well as cognitions, emotions and behaviour patterns (e.g. FTO or Taq1 A risk alleles, gut hormone functioning, high-energy density diets, dietary restraint). A significant feature of this model is that it can account for accumulating reports of both *increased* activation of reward-related brain areas in response to food cues, and *decreased* activation in response to food ingestion: for some individuals, long-term exposure to highly palatable high-calorie foods leads to down-regulation of dopamine receptors and therefore, lesser responses to food ingestion, while responsivity to food cues increases in order to motivate the consumption of larger amounts of even more palatable foods that will be sufficient to trigger the impoverished reward response (22). This perspective strongly argues for interventions to

moderate intake of highly palatable high-calorie foods early in life, so as to block this particular pathway to obesity. The model we have outlined is extremely simplified in its description of the underlying neuroanatomical pathways, and its representation of the iterative, interactive relationship between brain function and behaviour is limited. However, we believe it provides a useful conceptual framework for interpreting and designing research.

### Methodological issues – imaging

While the picture appears increasingly coherent at a macroscopic level, individual studies continue to produce different and sometimes discrepant results. This may be the result of certain methodological features. For example, while an advantage of PET is that it affords absolute measures of glucose metabolism and receptor density – and therefore a more direct assessment of brain activation – it gives poor spatial resolution and requires radiation exposure. In contrast, while MRI and fMRI have better spatial resolution and do not use radiation, they provide only an indirect measure of brain function. Studies using the two techniques may therefore be only cautiously compared. Individual findings regarding lateralization should also be evaluated carefully since conclusions regarding hemispheric specialization would require meta-analyses of large amounts of data that have not yet been generated, hence the omission of a discussion of lateralization in our review.

The anatomical properties of certain brain structures may also underlie some variations. For example, the proximity of the OFC to the air cavities of the sinuses may cause signal dropout, rendering it difficult to detect in studies that do not specify it as an ROI or use modified image acquisition methods (e.g. spiral pulse sequence, paramagnetic bite bar) to enhance detection. Although small, the hypothalamus is functionally differentiated, with the lateral part traditionally thought to mediate hunger, and the ventromedial part satiety. It may be easy to misunderstand its role without distinguishing these parts in acquisition and analysis. Different structures within the striatum are also functionally distinct. For example, while the NAc of the ventral striatum has long been considered the key area for dopaminergic reward, and therefore a likely candidate for abnormal functioning in obesity, many of the obesity studies find abnormalities in the dorsal region (e.g. caudate/putamen), associated with habit learning and addiction. Further differentiation between tasks may be necessary to disentangle the contributions of each part within the striatum.

### Methodological issues – stimuli

Differences in the stimuli used and the conditions of presentation may also explain differences between results. For example, each of the food picture studies uses different cues

and different control conditions, some of which were approximately matched for emotional valence and arousal (7,9,40) – improving the likelihood that the responses observed are specifically food related – and some of which were selected simply for neutrality (6). Another set of food cue studies uses conditioned cues for intake rather than pictures (23,57,62,70), affording greater experimental control but potentially less ecological validity, while another paradigm presents real foods, creating the opposite pattern of costs and benefits (38).

Further, whereas some studies take place after a substantial period of fasting (7), others occur after short or uncontrolled periods (6,9,40,71). Although much of the obesity literature highlights the occurrence of eating in the absence of hunger in the obese and therefore the importance of testing responses in the fed state, the longer fasting period may have the advantage of increasing stimulus salience and creating a more homogenous hunger state across subjects. Indeed, testing subjects in both fed and fasted states can lead to additional insights into the differentiation between phenotypes (56). Finally, within the studies that directly assess responses to food ingestion, the amount and type of food ingested may vary. For example the obese–lean differences in dlPFC activation observed in the studies by Le *et al.* (14,15) may have been influenced by the use of a large liquid meal, likely to produce sensory-specific, as well as absolute, satiety.

### Methodological issues – subjects

Sample differences between studies may also be important. For example, most studies have a BMI limit of 40 – probably due in part to the size and technical limitations of normal fMRI scanners – and therefore, certain studies including heavier individuals may be accessing a more extreme phenotype than the vast majority (21). It is also notable that overweight individuals (BMI 25–30) are normally omitted from studies comparing the obese and lean. This limits our knowledge of brain responses within this group and compresses the variation available for correlational analyses using BMI but increases power to detect weight-related differences within relatively small and therefore cost-effective samples.

Age and gender should also be considered. Thus far, evidence suggests that children and adolescents seem to show the same patterns as adults, and that men show the same patterns as women. However, the structural differences have yet to be replicated in children; doing so may help us understand whether the effects are prognostic indicators of obesity risk or whether they emerge only in the long-term obese. Studies of adolescents may also benefit by controlling for pubertal status, while studies of women should ideally control for menstrual status and oral contraceptive use, both known to affect appetite. The findings

on dietary restraint are probably most applicable to women, who are more likely to show this behaviour.

### Future directions

A number of exciting new developments may help to take this field forward. For example, some studies are attempting to break down the mechanisms underlying excessive food intake by moving beyond food intake and food cue paradigms into the realm of cognitive tasks designed to tap impulsive behaviour such as the go/no-go task (72), or tasks designed to tap responsiveness to other kinds of reward, e.g. monetary reward (48). Others are examining the association between more general traits (e.g. reward drive) and fMRI responses to food cues (73). As with all studies of aetiology, prospective longitudinal studies starting as early as possible in youth and tracking phenotypes into adulthood are needed to test the predictive value of neurological markers. New acquisition techniques such as arterial spin labelling, which directly measures cerebral perfusion by labelling arterial blood water, could aid research efforts by providing a more absolute indication of brain activity. Additionally, new statistical methods such as functional connectivity analyses (e.g. psychophysiological interaction analyses), which assess interactions between psychological states and functional coupling between brain areas, promise to reveal more about how areas within appetite-related networks communicate with and influence each other.

The neurobehavioural vulnerability model we have presented raises some interesting practical and ethical issues. For example, if infants or children at high genetic or early environmental risk for obesity show differences in hormone levels or neural responses to food that turn out to predict later weight gain, would it be desirable to design targeted pharmacological or behavioural interventions to reduce obesity risk? Educational interventions to encourage focus on internal (similar to homeostatic) vs. external (similar to hedonic) cues, slow eating rate or improve cognitive control could potentially be implemented. Educating individuals and parents about neurological tendencies may help to reduce perceptions of blame and guilt, and promote appreciation of the importance of environmental control, particularly for those already obese or at risk for becoming obese.

### Conflict of Interest Statement

No conflict of interest was declared.

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