Brain imaging studies of appetite in the context of obesity and the menstrual cycle

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BACKGROUND: Obesity affects many aspects of health, including reproduction. Despite unrelenting warnings about the health consequences of obesity, its prevalence continues to rise. Beginning with the discovery of leptin in 1994, the endocrinology of energy homeostasis has been significantly advanced. More recently, brain imaging studies have been providing novel insights into homeostatic and hedonic aspects of human ingestive behavior.

METHODS: A comprehensive MEDLINE search was conducted on the topic of neuroendocrine control of ingestive behavior with an emphasis on functional magnetic resonance imaging studies. Additional articles were collected by hand searching the bibliographies of all relevant articles retrieved.

RESULTS: This review describes recent advances in our understanding of endocrine signals that respond to acute and chronic energy states and regulate ingestive behavior so as to achieve a balance between energy intake and energy expenditure. Recently published brain imaging studies, describing the neural networks that process endocrine signals of energy state and hedonic cues associated with highly palatable foods, are highlighted. Brain responses to food cues are described in the context of appetite changes during the menstrual cycle both in normal physiology and under the conditions anorexia nervosa and bulimia nervosa.
**CONCLUSIONS:** The prevalence of obesity belies the plethora of endocrine signals in place to ensure energy homeostasis. However, satiety signals appear to be counteracted by hedonic signals derived from highly palatable foods typical of today’s diet. A better understanding of the interaction between homeostatic and hedonic signals is needed to devise effective strategies for dealing with obesity. Menstrual cycle dependent changes in brain responses to food cues may provide insight into the normal physiological control of ingestive behavior as well as dysfunctional regulation associated with disordered eating.

**Key words:** obesity / functional magnetic resonance imaging / appetite / homeostatic / menstrual cycle

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**Introduction**

**Obesity**

The alarm about increased obesity rates was sounded more than 20 years ago. The prevalence of obesity has more than doubled in the 1980s and 1990s (Flegal et al., 2002). Today, about two-thirds of the USA adult population is either overweight [defined as having a body mass index (BMI) = 25–29.9 kg/m²] or obese (BMI ≥ 30 kg/m²). Over 30% of the population is obese whereas 5% of the population is extremely obese (BMI ≥ 40 kg/m²). The prevalence of childhood obesity (defined as ≥95th percentile) is most concerning. On the basis of the National Health and Nutrition Examination Survey conducted in 1999–2000, childhood obesity occurred at a rate of 17%, which is a 3–4-fold increase compared with the survey conducted in 1963–1970 (Ogden et al., 2006). Whereas type II diabetes was once considered a disease of adults (adult onset diabetes), its incidence in youth, particularly in minorities, has increased markedly and now accounts for about one-third of all new cases of diabetes in children (Rosenbloom et al., 1999). Because obesity is associated with an increased risk of cardiovascular disease and cancer in addition to diabetes (Must et al., 1999), it has been suggested that the average life span could decline for the first time in recorded history (Olshansky et al., 2005). The financial consequences of obesity in the USA in terms of provision of health care as well as the indirect costs of reduced productivity were estimated in 2004 to be between 75 and 100 billion dollars (Finkelstein et al., 2004; Allison et al., 1999). The direct costs of obesity in the UK in 2002 were estimated to be 6 billion pounds annually (Rayner and Scarborough, 2005). The World Health Organization stated in 2003 that obesity is one of the most serious world health problems (Kelner and Helmuth, 2003).

**Reproductive effects of obesity**

The incidence of several pregnancy associated complications (pre-eclampsia, gestational diabetes, hypertension and Cesarean section) and birth defects (cardiac and neural tube) are increased 2–5-fold in obese women (Watkins et al., 2003; Cedergren, 2004; Weiss et al., 2004). Obesity is a contributing factor in anovulatory infertility. It is estimated that fecundity progressively declines by about 4% for each BMI value above 29 kg/m² (The Practice Committee of the American Society for Reproductive Medicine, 2008). Conversely, weight loss improves fecundity (Clark et al., 1998). *In-vitro* fertilization is less effective in the obese patient. Compared with non-obese women, a pregnancy odds ratio was calculated as 0.75 for obese women and 0.5 for women in the very obese category (Wang et al., 2002b). Obese women also have a higher miscarriage rate (Wang et al., 2002b; Fedorcsak et al., 2004). For these reasons, it has been recommended that fertility therapy be delayed until significant weight loss is achieved (Balen et al., 2006). However, such a recommendation needs to be accompanied by a comprehensive and effective plan towards achieving the stated weight loss goals that is tailored to the patient. Clearly we do not understand the regulation of ingestive behavior well enough to devise effective strategies for treating or preventing obesity in today’s obesogenic environment that is characterized by ready access to highly palatable calorically dense foods and a sedentary work and leisure environment.

**Article overview**

This article will review our current understanding of appetite regulation. The endocrine factors that signal energy state and affect ingestive behavior, so as to achieve a balance between energy intake and energy output (homeostatic regulation), are reviewed, and this is followed by a discussion of non-homeostatic regulation of ingestive behavior, also known as hedonic eating. Recent imaging studies that describe how the brain responds to food cues will be discussed in detail. Because food ingestion changes during the menstrual cycle, we have initiated functional neuroimaging studies in order to understand the mechanisms whereby ovarian steroids influence ingestive behavior. This review will provide the reader with an up to date summary of recent developments in appetite regulation, with an emphasis on brain imaging studies that provide novel insights into the biology and psychology of human ingestive behavior.

**Methods**

English language journals were searched using PubMed. Articles were retrieved using the following mesh terms or keywords: obesity, appetite, hunger, satiety, eating, anorexia nervosa, homeostatic, hedonic, reward, functional magnetic resonance imaging, functional magnetic resonance imaging (fMRI), food addiction, dopamine, menstrual cycle, estrogen, progesterone and corticolimbic. Additional articles were collected by hand searching the bibliographies of the most relevant retrieved articles and using the ‘cited by’ and ‘similar articles’ feature available either through PubMed or the electronic version of retrieved articles.

**Regulation of eating**

**Neuroendocrine (homeostatic) control**

There has been a significant advancement in our knowledge about appetite regulation and energy balance in the past 15 years, beginning with the exciting discovery of leptin in 1994 (Zhang et al., 1994). In addition, a number of gastrointestinal hormones that change in response to a meal have been discovered subsequent to leptin. The
following is a partial list of factors involved in energy balance regulation, along with a brief description of their physiology.

(i) Leptin is a 16 kDa cytokine produced by the adipocyte. The discovery of leptin in 1994 generated much excitement due to the remarkable weight loss achieved by leptin replacement in a leptin deficient mouse strain called the ob-/ob- mouse (Campfield et al., 1995; Halaas et al., 1995; Pellemounter et al., 1995). Although leptin moderately inhibited food intake and reduced weight in animals that were not leptin deficient, most clinical trials have not demonstrated significant weight loss in obese humans (Hulshorn et al., 2002; Heymsfield et al., 1999; Zelissen et al., 2005). In contrast, the same leptin formulation melted away the fat when given to obese humans who were leptin deficient due to a rare genetic mutation (Farooqi et al., 1999, 2002; Campfield et al., 1995; Williamson et al., 2005). Because leptin levels in the circulation are already increased in the vast majority of obese individuals, it is not surprising that elevating leptin levels further had little effect. It was concluded that chronically elevated leptin levels lead to leptin resistance which contributes to leptin’s inability to induce weight loss in the obese (Scarpone and Turner, 2001). Although leptin is no longer considered a potential first line therapy for weight loss, it has been proposed that leptin may be effective as an adjunct for weight loss maintenance, presumably after leptin sensitivity has been normalized (Fogteloow et al., 2003). The consensus is that low rather than high leptin levels provide important information about energy balance. Low leptin levels signal a chronic negative energy state, resulting in energy conservation through reduced metabolism and inhibition of the reproductive axis (Ahima et al., 1996). Stimulation of the reproductive axis occurred when exogenous leptin was administered for 3 months to lean anovulatory women (Welt et al., 2004). A low leptin concentration is a stimulus to eat whereas a chronically elevated leptin concentration may have little effect on food intake.

(ii) Adiponectin, like leptin, is a cytokine produced by adipocytes, but unlike leptin, adiponectin levels are inversely correlated with adiposity. Adiponectin’s role in energy balance is controversial. Although elevated adiponectin is associated with a lean phenotype, it may or may not inhibit food intake, and disruption of adiponectin signaling, unlike leptin, does not result in an obese phenotype (Henry and Clarke, 2008). The focus of adiponectin is more on aspects of metabolic syndrome other than appetite regulation. Adiponectin increases insulin sensitivity and its anti-inflammatory action may inhibit vascular wall injury and atherosclerosis (Diez and Iglesias, 2003; Goldstein and Scalia, 2004).

(iii) Cholecystokinin (CCK) was the first gut hormone identified to have satiety effects (Gibbs et al., 1973). CCK is released within minutes of eating, inhibits gastric emptying, and is thought to play a role in meal termination. CCK appears to inhibit food intake through multiple mechanisms. The satiety effects of CCK are mediated in part by vagal afferents (Moran and Kinzig, 2004). In addition, CCK receptors are present in the hypothalamus, and intra-hypothalamic injection of CCK can inhibit food intake (Blevins et al., 2000). Rats that lack CCK receptors are obese (Moran et al., 1998). Despite these compelling results, chronic CCK administration was ineffective in reducing food intake and weight. Although CCK reduced meal size, meal frequency was increased (West et al., 1984). CCK agonists are no longer considered to be viable therapeutic options (Fong, 2005).

(iv) Peptide YY (PYY) has garnered considerable attention as a physiological regulator of appetite. PYY1-36 is produced in L cells of the distal ileum and colon and is released in the post-prandial period (McFadden et al., 1989). PYY circulates primarily as PYY3-36 following cleavage of PYY1-36 by dipeptidyl peptidase (Grandt et al., 1994; Le Roux et al., 2006). Several studies showed that PYY3-36 administration inhibited food intake in rodents as well as in human and non-human primates (Batterham et al., 2002; Challis et al., 2003; Cox and Randich, 2004; Halatchev et al., 2004; Chelikani et al., 2005; Degen et al., 2005; Koegler et al., 2005; Moran et al., 2005; Le Roux et al., 2006; Papadimitriou et al., 2007). Circulating PYY levels are reduced in obese humans, whereas plasma concentrations are increased with anorexia nervosa (Misra et al., 2006; Pflüger et al., 2007) and disordered eating (Scheid et al., 2009). Although it was initially proposed that PYY might contribute to these phenotypic changes, this appears not to be the case since PYY levels were reduced in a rat model of diet induced obesity (Le Roux et al., 2006). In addition, PYY levels were increased following bariatric surgery (Ballantyne, 2006; Meguid et al., 2008), but these changes may result from weight loss rather than cause weight loss. A limited number of clinical trials do not support PYY as a viable weight loss drug. Subcutaneous PYY3-36 administration at doses well tolerated did not acutely reduce food consumption. Intranasal PYY3-36 administration for 2 weeks did not promote weight loss, whereas higher PYY doses that did result in reduced food consumption were associated with nausea (Gantz et al., 2007; Sloth et al., 2007b, a).

(v) Glucagon like peptide-1 (GLP-1) is a post-translational product of the pre-proglucagon gene. GLP-1 is released from the L cells of the intestines in response to carbohydrates. GLP-1 inhibits gastric emptying, inhibits glucagon and inhibits food intake in rodents (as reviewed in Murphy et al., 2006) and humans (Gutzwiller et al., 1999; Edwards et al., 2001). Administration of GLP-1 together with PYY3-36 inhibited food intake in an additive fashion in both rodents and man (Neary et al., 2006). In addition to inhibiting appetite, GLP-1 has a significant effect on glucose homeostasis. Exenatide, a long acting GLP-1 agonist approved for treating type II diabetes, inhibited glucagon, increased insulin, improved glycemic control and reduced weight in a 30 weeks clinical trial (Buse et al., 2004; DeFronzo et al., 2005).

(vi) Oxyntomodulin, like GLP-1, is produced in the L cells from the pre-proglucagon gene. Oxyntomodulin is released post-prandially, inhibits gastric emptying and reduces food intake (as reviewed in Murphy et al., 2006). Oxyntomodulin may act at the GLP-1 receptor to inhibit food intake. In addition to suppressing appetite, oxyntomodulin increases energy expenditure (Wynne et al., 2006).

(vii) Amylin is a 37 amino acid peptide produced in β cells of the pancreas and is released along with insulin after a meal.
Amylin slows gastric emptying and inhibits glucagon release. Exogenous amylin reduces food intake in rodents (Lutz, 2005). The resulting weight loss is primarily due to a reduction in fat mass (Roth et al., 2006). Pramlintide, a long acting amylin agonist, when used in combination with insulin, improved glycemic control and prevented the weight gain that normally accompanies insulin therapy (Pullman et al., 2006). Pramlintide therapy (compared with placebo) together with lifestyle modification produced significant and sustained weight loss (Smith et al., 2008).

(viii) Ghrelin is a 28 amino acid peptide, discovered in 1999, which binds to the growth hormone secretagogue receptor (Kojima et al., 1999). In addition to stimulating growth hormone, exogenous ghrelin stimulates food intake (the only known circulating orexigenic hormone). Ghrelin is released from the fundus of the stomach and appears to be a physiological regulator of eating (Wren et al., 2001; Wang et al., 2002a). Ghrelin levels are highest just before a meal and decline shortly after food ingestion. Ghrelin levels are reduced with obesity and may reflect dysregulated ghrelin secretion as a result of chronic hyperphagia. In contrast, ghrelin is increased in Prader–Willi patients and has been implicated in the hyperphagia of this syndrome (Cummings et al., 2002a). A dramatic reduction in ghrelin levels following gastric bypass surgery may contribute to the success of this procedure in achieving long-term weight loss (Cummings et al., 2002b). Ghrelin agonists may prove useful in treating cachexia whereas antagonists may be developed as a medical treatment for obesity. The reader is referred to (Jayasena and Bloom, 2008) for more details about these gut derived hormones.

### Hypothalamic detection of energy balance signals

The hypothalamus plays a critical role in the receipt and transduction of the aforementioned circulating signals of energy state. Receptors for these hormones are present within hypothalamic peptidergic neurons that affect ingestive behavior. Activation of neurons, within the arcuate nucleus of the hypothalamus, that co-express neuropeptide Y (NPY) and agouti regulated peptide (AgRP) play a pivotal role in stimulating food intake, whereas activation of arcuate neurons that co-express pro-opiomelanocortin (POMC) and cocaine-amphetamine regulated transcript (CART) inhibit food consumption (Schwartz et al., 1996, 1997; Elias et al., 1998, 1999; Baskin et al., 1999; Cowley et al., 2001; Halatchev et al., 2004) (Fig. 1). These neurons contain receptors for leptin (Mercer et al., 1996), PYY, GLP-1 (Christophe, 1998) and ghrelin (Nakazato et al., 2001; Zigman et al., 2006). Leptin, PYY$_{3-36}$ and GLP-1 inhibit food intake by inhibiting NPY/AgRP neurons whereas ghrelin stimulates food intake by stimulating NPY/AgRP neurons. In contrast, leptin, PYY$_{3-36}$ and GLP stimulate POMC/CART neurons whereas ghrelin inhibits them. A coordinated neurochemical response is ensured by inhibitory synaptic communication between NPY/AgRP and POMC/CART neurons (Broberger et al., 1997; Elmquist et al., 1998; Elias et al., 1999). In addition to the arcuate nucleus, the lateral hypothalamus regulates energy intake. The neuropeptides Orexin A and B (also called hypocretins) are synthesized in the lateral hypothalamus and as their name implies, stimulate food intake (de Lecea et al., 1998; Sakurai et al., 1998). Orexins are also important in wakefulness as orexin knockout animals are narcoleptic (Siegel, 1999). Orexin positive neurons originating in the lateral hypothalamus project to the amygdala, ventral tegmental area, and the nucleus accumbens and may be responsible for reward related eating (Berriidge, 1996; Boulrel and de Lecea, 2008). The precise mechanisms whereby stimulation or inhibition of orexigenic NPY/AgRP and orexin neurons and anorexigenic POMC/CART neurons within the arcuate nucleus and lateral hypothalamus lead to a change in ingestive behavior is poorly understood. These peptidergic neurons project to the paraventricular nucleus within the hypothalamus as well as to extrahypothalamic areas. In addition, glutamatergic and GABAergic efferents mediate the effect of these neuropeptides on eating through projections to corticolimbic regions (Zheng et al., 2003). However, the mechanism whereby these projections influence ingestive behavior is yet to be defined.

### Hedonic eating and the corticolimbic brain

Eating is a complex behavior that is not simply turned on or turned off by hormones that signal energy state. The pleasures derived from the

![Diagram](https://academic.oup.com/humupd/article-abstract/16/3/276/640665/16327664665)
taste, smell and texture of food promote eating despite the brain’s reception of positive energy balance signals (increased concentrations of leptin, insulin, glucose, amylin, PYY, GLP-1 and oxyntomodulin, and decreased concentrations of ghrelin). This type of eating is classified as hedonic eating in distinction to homeostatic eating. As its description implies, hedonic eating can override the satiety effect of positive energy balance signals (Saper et al., 2002; Harrold and Williams, 2003; Kringelbach, 2004; Mela, 2006; Lowe et al., 2009).

Many regions of the corticolimbic and mesolimbic brain involved in learning and memory, emotion and reward processing have been implicated in hedonic eating. These include the prefrontal cortex, lateral and medial orbitofrontal cortex, anterior cingulate, insula, hippocampus, amygdala, nucleus accumbens (ventral striatum), caudate/putamen (dorsal striatum), pallidum, ventral tegmental area and fusiform. A comprehensive description of the complex anatomical and functional connectivity of these brain regions is beyond the scope of this review, and the reader is referred to an excellent review (Morgane et al., 2005). Because the regions included in the corticolimbic brain are highly interconnected and are not limited to the control of ingestive behavior, it is simplistic to ascribe stimulatory or inhibitory ingestive behavioral effects to specific regions. Instead broader descriptors such as reward, cognition, executive function and gustatory are used to describe how brain regions within the corticolimbic network affect ingestive behavior. Figure 1 is a simplified depiction of the brain regions that regulate homeostatic and hedonic eating and their interconnections. The prefrontal cortex and the amygdala are important in reward evaluation, inhibitory control and executive decision-making (Schoenbaum et al., 1998; Petrovich et al., 2002; Gottfried et al., 2003; Holland and Gallagher, 2004; Kringelbach and Rolls, 2004; Kringelbach, 2004; Rolls, 2004; Petrovich et al., 2005; Petrovich and Gallagher, 2007). The amygdala receives input from the ventral tegmental area (dopaminergic), insula and fusiform (visual cortex). The insula, considered to be the primary gustatory cortex, receives visceral information by way of afferent inputs from the nucleus tractus solitarius and lateral parabrachial nucleus. In addition to innervating the amygdala, the insula sends efferent projections to the anterior cingulate, orbitofrontal cortex, striatum, pallidum, thalamus, lateral hypothalamus and nucleus accumbens. The nucleus accumbens and adjacent ventral pallidum may affect ingestive behavior by integrating hedonic signals from mesolimbic/corticolimbic regions with homeostatic input from the hypothalamus (Berthoud, 2002; Kelley, 2004; Abizaid et al., 2006).

**Imaging networks affecting ingestion**

Although regulation of ingestive behavior can be compartmentalized as homeostatic or hedonic based on neuroanatomical and functional parameters, communication between these two compartments determines when, what and how much we eat. Our ability to study the neural networks that influence ingestive behavior in humans has improved immensely with significant advances in imaging technology in the past 15 years. These exciting neuroimaging results are summarized below.

**Functional magnetic resonance imaging**

Functional MRI is a powerful tool for studying brain activation. Functional MRI provides an indirect measure of activation by quantifying the Blood Oxygen Level Dependent (BOLD) signal. The BOLD signal is derived from changes in the ratio of oxyhemoglobin to deoxyhemoglobin. Because deoxyhemoglobin is paramagnetic, changes in this ratio can be detected in the MRI magnetic field. Blood flow is increased to activated brain regions in order to meet the increased metabolic demands. This hemodynamic response causes deoxyhemoglobin levels to decline and this change is detected in the form of a BOLD signal (Ogawa et al., 1990; Arthurs and Boniface, 2002; Logothetis and Wandell, 2004; Nair, 2005). In recent years, this technology has been applied to the study of appetite. There are now a significant number of imaging studies describing the brain’s response to various food cues. Response differences achieved under fed or fasted conditions in normal weight and obese subjects are providing new insights into the control of ingestive behavior.

**Stimulus protocols**

Food cues used in fMRI protocols to elicit a BOLD response include taste, smell and sight. Because of their relative ease of delivery, visual food cues consisting of either actual food or pictures of food are commonly used. Visual food cues are effective because stimuli associated with primary rewards acquire motivational potency and trigger wanting due to their acquired ability to stimulate reward circuits (classical conditioning). Brain activation due to visual food cues is quantified by subtracting the BOLD signal elicited by control pictures (pictures of items not associated with food or eating) from BOLD signal that occurs while viewing pictures of food.

**Brain responses to visual food cues**

The corticolimbic brain regions that are consistently activated by visual food cues include the prefrontal cortex, lateral and medial orbitofrontal cortex, amygdala, hippocampus, parahippocampus, anterior cingulate, insula, hypothalamus, striatum, pallidum, ventral tegmental area and fusiform (Tataranni et al., 1999; LaBar et al., 2001; Killgore et al., 2003; Pelchat et al., 2004; Wang et al., 2004; St-Onge et al., 2005; Beaver et al., 2006; Holsen et al., 2006; Killgore and Yurgelun-Todd, 2006; Porubska et al., 2006; Uher et al., 2006; Baicy et al., 2007; Cornier et al., 2007; Farooqi et al., 2007; Rolls and McCabe, 2007; Rothermund et al., 2007; Malik et al., 2008; Stoeckel et al., 2008).

Although there are significant differences in the regions reported to be activated by visual food cues in the individual studies, it is likely that experimental variables such as stimulus paradigms, gender, hunger level and adiposity are at the root of these differences. Collectively, these studies show that brain regions involved in processing reward, emotion and cognition are activated when subjects are exposed to food pictures. The fusiform, amygdala, hippocampus, insula, lateral orbitofrontal cortex and dorsal striatum are activated by visual food cues in the majority of studies. It is instructive to examine how brain responses to visual food cues are affected by hunger, adiposity and metabolic/endocrine cues in order to begin understanding how the corticolimbic brain influences ingestive behavior.
Influence of adiposity and hunger

Two recent fMRI studies reported a greater brain response to food pictures in obese women compared with normal weight women (Rothemund et al., 2007; Stoeckel et al., 2008). Both studies reported greater activation in the lateral orbitofrontal cortex, insula, hippocampus, anterior cingulate and dorsal striatum of obese compared with normal weight women in response to pictures of high calorie foods compared with low calorie foods or control pictures. BMI was positively correlated with the degree of activation elicited by high calorie food pictures specifically in several regions including the dorsal striatum, anterior insula, claustrum, posterior cingulate, post-central and lateral orbitofrontal cortex. These studies indicate that brain regions involved in learning and habit formation, emotion and motivation are stimulated by food stimuli to a greater extent in obese women. One of the studies observed significantly more activation extending to the medial prefrontal cortex, medial orbitofrontal cortex, ventral pallidum, amygdala and ventral striatum (Stoeckel et al., 2008). Greater activation was attributed to subjects being hungry at the time of the scan, whereas hungry subjects were explicitly excluded in the other study (Rothemund et al., 2007). The conclusion that food pictures have greater salience in the fasted state and evoke a greater BOLD response is supported by a previous fMRI study in which normal weight male and female subjects had greater activation in the amygdala, parahippocampus and anterior fusiform in the fasted state (LaBar et al., 2001). Another study reported that food pictures caused more activation in the inferior temporal visual cortex, posterior parietal cortex, premotor cortex, hippocampus and hypothalamus in subjects maintained on an eucaloric diet compared with subjects who ate in excess for several days prior to scanning (Cornier et al., 2007). When food cravings were induced by placing participants on a bland diet for 2 days before undergoing fMRI, more activation was seen in the hippocampus, insula and caudate when subjects imagined their favorite foods (Pelchat et al., 2004). Striking differences were observed when responses in healthy weight controls were compared with individuals with Prader–Willi Syndrome, a genetic disorder characterized by hyperphagia-induced early onset obesity. Whereas normal weight controls had greater activation in the amygdala, orbitofrontal cortex, medial prefrontal cortex and frontal operculum in response to food pictures in the pre-prandial state compared with the post-prandial state, Prader–Willi patients had greater activation in the amygdala, orbitofrontal cortex, insula, parahippocampus and fusiform post-prandially (Holsen et al., 2006). Another study reported that food pictures presented after an oral glucose load activated the medial prefrontal cortex of Prader–Willi patients, but not normal weight controls (Miller et al., 2007). These results suggest that the salience of food cues is not only maintained but increased in Prader–Willi patients despite having eaten and that this abnormal response may contribute to hyperphagia and obesity.

Positron emission tomography (PET) imaging studies were the first imaging studies of appetite. Differences between PET and fMRI in terms of signal detection, as well as spatial and temporal resolution, present some challenges when comparing results achieved by the two imaging modalities. The first PET imaging study of appetite compared the regional cerebral blood flow (rCBF) in response to food images in normal weight and obese women. Food images induced a greater rCBF in the parietal and temporal cortices of obese women compared with lean women (Karhunen et al., 1997). Subsequent PET studies compared rCBF in lean and obese men and women before and after consuming a liquid meal (Gautier et al., 2000, 2001). Meal-induced satiation increased rCBF to the prefrontal cortex in obese and normal weight men and women (obese men > lean men) and reduced blood flow to the thalamus, insula, parahippocampus and cerebellum of lean and obese women and to the hippocampus, striatum and cerebellum of obese men more than lean men. Cerebral blood flow to the hypothalamus, amygdala, cingulate and nucleus accumbens was reduced in obese women, but not lean women, whereas reduced rCBF to the hypothalamus and thalamus was attenuated in obese men compared with lean men. These results indicate that brain activity in several corticolimbic regions as measured by cerebral blood flow is reduced after a meal and that responses are influenced by adiposity and gender (DelParigi et al., 2002). Increased activity in the prefrontal cortex in sated subjects was observed in men and women. The prefrontal cortex plays a role in suppressing inappropriate response tendencies, which in the context of the current study, would be eating when sated. The significance of greater activation of the prefrontal cortex in obese men is not clear, although another study reported that increased rCBF in the dorsolateral prefrontal cortex following a meal was greater in normal weight men compared with obese men (Le et al., 2006). Reduced rCBF to numerous corticolimbic regions in sated subjects compared with hungry subjects is consistent with fMRI studies showing activation of these regions by visual food cues. However, the significance of a meal-induced reduction in rCBF to the hypothalamus, amygdala, cingulate and nucleus accumbens in obese women, but not lean women, and the hippocampus, striatum and cerebellum of obese men more than lean men, is not readily apparent and perhaps paradoxical if one considers reduced rCBF to corticolimbic structures is part of the normal response to meal-induced satiation. Another group studied subjects whereas they imagined selecting food items from a restaurant menu. Subjects were normal weight men and were studied either after an overnight fast or within 1 h of having eaten. Increased rCBF in the hypothalamus, amygdala, striatum, insula and anterior cingulate cortex was observed when fasted, whereas increased activity in the lateral orbitofrontal and temporal cortex was observed when sated (Hinton et al., 2004).

To summarize, numerous imaging studies show that brain activity as measured by BOLD signal or rCBF is increased in many brain regions involved in processing reward and motivation in response to food cues. Activation of the orbitofrontal cortex, insula, hippocampus, amygdala, anterior cingulate, and striatum are reported in most, but not all studies. A greater BOLD effect occurs in more brain regions in response to pictures of high calorie versus low calorie foods, and the response is more robust in obese subjects. The motivational potency of visual food cues is increased by hunger (Cabanac, 1971; Stoeckel et al., 2007). Increased brain activation in specific regions in association with hunger and obesity is presumably the basis for stimulating ingestive behavior. An abnormal brain response may predispose some individuals to obesity. However, in the absence of longitudinal studies, an equally feasible interpretation is that abnormal brain responses result from obesity. In this scenario, abnormal responses to food cues may contribute to maintenance of an obese state.
Imaging the effects of energy homeostasis hormones

Four recent studies described effects of leptin and ghrelin, two hormones with opposite effects on energy homeostasis, on brain activity elicited by visual food cues. Administration of the orexigen, ghrelin, in comparison to saline, produced greater activation of orbitofrontal cortex, prefrontal cortex, amygdala, insula and striatum when subjects viewed food pictures (Malik et al., 2008). These findings are depicted in Fig. 2. Furthermore, the magnitude of the response in the orbitofrontal cortex and amygdala correlated with increased hunger levels elicited by ghrelin, suggesting that the BOLD effects and behavioral effects of ghrelin were related. Two fMRI studies compared responses to visual food cues in leptin deficient patients whereas on or off leptin replacement therapy (Baicy et al., 2007; Farooqi et al., 2007). Food pictures elicited a greater BOLD response in the insula, parietal lobe, and striatum and increased hunger ratings when patients suspended leptin therapy for a few weeks, whereas activation in the prefrontal cortex was increased and hunger ratings were reduced in the same patients when leptin replacement therapy resumed. A third leptin study measured brain responses to visual food cues in obese patients who had achieved a 10% reduction in body weight. Patients were injected twice daily with either saline or leptin in a crossover design (Rosenbaum et al., 2008). Visual food cues presented during the placebo arm following weight loss produced greater activation of the brainstem, culmen, parahippocampal gyrus, inferior and middle frontal gyri, middle temporal gyrus and lingual gyrus, but less activation in the hypothalamus, cingulate gyrus and middle frontal gyrus when compared with activation elicited prior to weight loss. These responses were reversed when leptin levels were reinstated to pre-weight loss levels with exogenous leptin, indicating that these specific brain regions are responsive to changes in leptin concentrations. Collectively, these four studies indicate that leptin and ghrelin, in addition to their effects on the hypothalamus, influence ingestive behavior through effects on corticolimbic structures that evaluate the emotional, memory, taste and reward aspects of food.

Another recent fMRI study examined the effect of the gut derived satiety factor PYY on brain activity (Batterham et al., 2007). Unlike the previously described studies, this study did not use visual food cues. Infusion of PYY3-36 that produced post-prandial concentrations of PYY increased the BOLD signal in the caudal orbitalis and hypothalamus and significantly reduced the number of calories consumed when subjects were given unlimited access to a buffet meal subsequent to the scan session. The magnitude of the BOLD response in the hypothalamus was inversely correlated with the number of calories eaten, suggesting that PYY-induced activation of the hypothalamus was in part responsible for inhibiting appetite. Although PYY infusion increased BOLD signal in the hypothalamus, hypothalamic activity (unlike the orbitofrontal cortex) did not correlate with food consumption. This finding demonstrates that a vital component of homeostatic control of eating, namely the postprandial rise in PYY, may inhibit eating by activating a hedonic-corticolimbic region (orbitofrontal cortex) rather than traditional homeostatic brain centers (hypothalamus).

Collectively, these five imaging studies suggest that the neural circuitry involved in metabolic homeostatic feedback is not limited to the hypothalamus and brainstem, but involves hedonic brain regions. These effects may be indirect through receptor signaling in the hypothalamus or direct since receptors for leptin, ghrelin and PYY are present in the ventral tegmental area, amygdala and hippocampus (Gustafson et al., 1997; Dumont et al., 1998; Kaga et al., 2001; Figlewicz et al., 2003; Diano et al., 2006; Hommel et al., 2006). These studies also demonstrate the utility of fMRI to study human brain responses to metabolic signals, either separately or in combination with visual food cues, thus providing a powerful method to study the interactions between homeostatic and hedonic signals controlling eating.
Appetite regulation in women

Menstrual cycle related changes in appetite

Significant changes in food intake during the menstrual cycle have been documented in both human and non-human primates. Menstrual cycle dependent changes in women and in rhesus monkeys documented by food diaries or food weighing indicate that food intake is reduced in the periovulatory phase and increased during the luteal phase (Czaja, 1978; Rosenblatt et al., 1980; Dalvit, 1981; Kemnitz et al., 1984; Lissner et al., 1988; Gong et al., 1989; Lyons et al., 1989; Buffenstein et al., 1995; Barr et al., 1995; Dye and Blundell, 1997; Reimer et al., 2005). Figure 3 shows food intake normalized to the day of the luteinizing hormone surge in rhesus monkeys. Food intake reaches a nadir around the time of ovulation when estrogen is elevated and progesterone is low and increases following ovulation when progesterone is dominant. Increased food intake premenstrually has been documented in women diagnosed with premenstrual dysphoric syndrome (Bowen and Grunberg, 1990; Cross et al., 2001; Reed et al., 2008).

Effect of ovarian steroids

Prior to primate studies that showed menstrual cycle dependent changes in food intake, rodent studies demonstrated estrous cycle dependent changes in food intake and that changes in ovarian steroids during the estrous cycle were responsible for changes in food consumption. Ovariectomy led to increased food intake and weight gain in rats. These effects of ovariectomy were reversed by estrogen, whereas the anorexigenic effect of estrogen was prevented when progesterone was co-administered (Tarttelin and Gorski, 1973; Jankowiak and Stern, 1974; Wade, 1975; Blaustein and Wade, 1976; Wade et al., 1985). This effect of ovariectomy and gonadal steroid replacement was confirmed in monkeys (Kemnitz et al., 1989). The effects of ovariectomy and estrogen replacement on food intake are transient, whereas their effects on weight remain, suggesting peripheral effects of chronic ovarian steroid exposure (Wade and Gray, 1979). Gonadal steroid replacement in post-menopausal women did not affect food intake or body weight (Reimer et al., 2005), but did reduce abdominal fat whereas not affecting total body fat (Haarbo et al., 1991; Reubinoff et al., 1995; Gambacciani et al., 1997). A systematic review found no evidence that either estrogen alone or in combination with a progestin affected weight gain in peri- or post-menopausal women (Kongnyuy et al., 2009). Since continuous hormone replacement does not mimic cyclical changes in ovarian steroids, a lack of effect of hormone replacement on weight in the clinical setting is not in conflict with the conclusion that ovarian steroids influence energy balance during the menstrual cycle.

Ovarian steroid hormones site of action

Ovarian steroid effects on food intake and body weight were first reported in 1974. It is remarkable that the mechanisms that cause this large physiological change in ingestive behavior in humans are so poorly understood many years later

(i) Leptin, ghrelin and PYY levels during the menstrual cycle: Numerous studies have measured leptin levels throughout the menstrual cycle. Most studies report a slight elevation during the luteal phase as compared with the follicular phase (Hardie et al., 1997; Shimizu et al., 1997; Riad-Gabriel et al., 1998; Teirmann et al., 1998; Cella et al., 2000; Ludwig et al., 2000; Geisthovel et al., 2004; Wunder et al., 2006; Asimakopoulos et al., 2009). Increased leptin during the luteal phase may signal a period of positive energy balance. Thus, the pattern of leptin secretion during the menstrual cycle may reflect (rather than affect) changes in caloric intake. Two studies noted a small increase in leptin during the late follicular phase compared with the early follicular phase which could explain reduced food intake during the periovulatory phase (Geisthovel et al., 2004; Asimakopoulos et al., 2009), but this was not observed in the majority of studies. There is only one report on ghrelin levels during the menstrual cycle, and it showed that ghrelin was unchanged (Dafopoulos et al., 2009). There are no reports on PYY levels during the menstrual cycle. We measured PYY levels in rhesus monkeys on a daily basis both pre- and post-prandially and found no pattern of change during the menstrual cycle (Van Vugt, unpublished).

(ii) Estrogen receptors: The site of action and the specific neurotransmitters/neuromodulators mediating these steroid effects have not been established. Both alpha estrogen receptors (ER\(\alpha\)) and beta estrogen receptors (ER\(\beta\)) are present in the brain. ER\(\alpha\) is concentrated in the hypothalamus, whereas ER\(\beta\) is distributed more broadly in the brain (Shughrue et al., 1997; Laflamme et al., 1998; Kuiper et al., 1998). The hippocampus, substantia nigra, dorsal raphe, striatum, nucleus accumbens and pontine nucleus are densely labeled with ER\(\beta\) mRNA (Gundlah et al., 2000; Ostlund Hann et al., 2003). Co-labeling of dopamine and ER\(\beta\) showed that both dopamine and non-dopamine neurons were ER\(\beta\) positive (Creutz and Kritzer, 2002). Ovariectomy
Reduced dopamine binding in the striatum and the nucleus accumbens core (Le Saux et al., 2006). This effect was reversed by estradiol or an ERβ agonist, but not by an ERα agonist, indicating that the stimulatory effects of estrogen on dopamine receptors were mediated through ERβ rather than ERα. This conclusion is supported by the finding that a specific ERβ agonist stimulated amphetamine-induced place preference in ovariectomized rats (Silverman and Koenig, 2007). Reduced dopamine signaling in the reward circuit of ovariectomized rats could lead to a compensatory increase in food consumption. However, the report that estrogen replacement inhibited food intake and reduced body weight in ovariectomized wild type and ERβ knockout mice, but not in ERα knockout mice is contrary to the conclusion that ERβ mediates estrogen-induced anorexia (Geary et al., 2001). It is conceivable that estrogen signaling at ERα is important for homeostatic control of food intake whereas estrogen signaling at ERβ is more relevant to hedonic eating.

(iii) Other possible neuroendocrine mechanisms: An interaction between estrogen and leptin is suggested by the considerable overlap in the distribution of receptors for estrogen and leptin within the hypothalamus (Diano et al., 1998). Estrogen replacement increased leptin-induced anorexia in ovariectomized rats (Clegg et al., 2006). However, this apparent increase in leptin sensitivity was not associated with increased leptin receptor number. Currently, there is no consensus on whether estrogen stimulates or inhibits leptin receptor expression. Additionally, the report that estrogen can induce anorexia in leptin deficient mice suggests involvement of mechanisms in addition to leptin (Tritos et al., 2004). Increased sensitivity to CCK-induced meal termination has been proposed (Asarian and Geary, 1999). Estrogen potentiated CCK-induced anorexia, and estradiol replacement to ovariectomized rats increased CCK-induced c-fos expression (a marker of neuronal activation) in the paraventricular nucleus, nucleus tractus solitarius and central amygdala (Eckel et al., 2002; Asarian and Geary, 2006). Involvement of serotonin is suggested by the observation that buspirone, a serotonin agonist, was more potent in stimulating food intake in the luteal phase compared with the follicular phase (Goodall et al., 1995).

Imaging menstrual cycle dependent changes in appetite

It appears that changes in leptin, PYY or ghrelin secretion do not explain changes in food intake that occur during the menstrual cycle. However, a change in sensitivity to these molecules remains a viable explanation for menstrual cycle dependent changes in food intake. Given the recent reports that brain effects of leptin, PYY and ghrelin can be measured with fMRI, it may be possible to use fMRI to study this question. We have undertaken brain imaging studies during different times of the menstrual cycle in order to determine if corticolimbic structures respond differently to visual food cues depending on menstrual cycle phase. Our results, whereas preliminary, indicate that visual food cues elicit a stronger BOLD response in several brain regions during the periovulatory period compared with that during the luteal phase of the menstrual cycle. Figure 4 contrasts activation between the two phases in 10 women. Food pictures activated the lateral orbitofrontal cortex, prefrontal cortex, hippocampus, amygdala and fusiform of women scanned in the periovulatory phase, whereas only the fusiform was activated in the luteal phase. Table I lists the regions that were significantly activated by the various contrasts. Most regions were activated by food pictures regardless of category (high versus low calorie foods). An exception was the insula, which was stimulated by pictures of low calorie foods, but not by high calorie foods in the follicular phase. Interestingly, the opposite effect was observed during the luteal phase as the insula was activated by high calorie foods, but not low calorie foods.

In a separate study, we asked women to rate the appeal of high calorie and low calorie foods on multiple occasions over the course of a menstrual cycle. Women rated pictures of high calorie foods as more appealing than low calorie foods in Weeks 1, 3 and 4, but not Week 2 of the menstrual cycle (Kim and Van Vugt, 2008). Since the insula was activated by low calorie but not high calorie food pictures when women were scanned during Week 2 of the menstrual cycle, whereas the insula was activated by high calorie but not low calorie foods.

Figure 4 Effect of menstrual cycle phase on brain activation. Women viewed pictures of food while undergoing functional magnetic resonance imaging during the late follicular phase and luteal phase of the menstrual cycle. Food pictures elicited greater activation in the follicular phase. Activation of the left orbitofrontal cortex (L. OFC), amygdala and hippocampus (not shown) in the follicular phase, but not luteal phase may influence reward perception of food cues and effect ingestive behavior (Van Vugt, unpublished).
food pictures in the luteal phase, we speculate that menstrual cycle dependent activation of the insula reflects menstrual cycle dependent changes in food appeal. An increased preference for low calorie foods in the second half of the follicular phase may contribute to the periovulatory reduction in caloric intake.

Table 1 Brain activation in response to visual food cues; influence of the menstrual cycle

<table>
<thead>
<tr>
<th>Follicular phase</th>
<th>ROI</th>
<th>Hemisphere</th>
<th>Cluster</th>
<th>t stat</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
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<td>7.23</td>
<td>−33, −54, −15</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>OFC</td>
<td>L</td>
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<td>7.75</td>
<td>−21, 30, −18</td>
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<tr>
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<td>21</td>
<td>6.25</td>
<td>−13, 0, −15</td>
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<tr>
<td></td>
<td>Amygdala</td>
<td>L</td>
<td>10</td>
<td>6.54</td>
<td>24, −3, −12</td>
</tr>
<tr>
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</tr>
<tr>
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<td>15</td>
<td>6.04</td>
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</tr>
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<td>R</td>
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<td></td>
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<td>Low cal versus control</td>
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<table>
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<th>Cluster</th>
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<th>MNI Coordinates</th>
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</thead>
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<tr>
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<tr>
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<tr>
<td>Insula</td>
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<td>5.3</td>
<td>−39, −6, 3</td>
<td></td>
</tr>
<tr>
<td>Low cal versus control</td>
<td>Fusiform</td>
<td>L</td>
<td>10</td>
<td>5.92</td>
<td>−33, −57, −21</td>
</tr>
</tbody>
</table>

ROI refers to region of interest; Cluster refers to the number of contiguous voxels which were activated; t-stat is a measure of activation in the peak voxel; MNI = Montreal Neurological Institute.

Effect of mood on brain response to food cues

Although ours is the first study to examine the effect of menstrual cycle phase on the BOLD response to visual food cues, another fMRI study similar to our own reported BOLD responses to food images in women. However, rather than menstrual cycle phase, affect was the primary variable of interest. The lateral orbitofrontal cortex was activated in response to high calorie food images, whereas the medial orbitofrontal cortex and insula were increased by low calorie food images in women reporting positive affect. The opposite activation pattern was observed in women reporting negative affect (Kilgore and Yurgelun-Todd, 2006). This differential effect of high and low calorie food pictures on the insula depending on mood parallels what we saw with menstrual cycle phase; i.e. the insula was activated by pictures of low calorie foods when women were periovulatory (like women who reported positive affect), but was activated by high calorie foods when subjects were scanned in the luteal phase (like women who reported negative affect). Since negative affect occurs more frequently during the luteal phase (Cockerill et al., 1994), menstrual cycle phase may have been a contributing factor.

Imaging eating disorders

Binge eating, bulimia nervosa and anorexia nervosa are extreme eating disorders that are more prevalent in women than in men (Hudson et al., 2007). A study comparing responses in subjects with disordered eating (binge eating disorder or bulimia nervosa) reported that food pictures activated the orbitofrontal cortex, anterior cingulate and insula in both patient groups and in controls, but overweight binge eaters had a stronger response in the medial orbitofrontal cortex compared with overweight healthy controls (Schienle et al., 2009). The authors suggest that increased activation of the medial orbitofrontal cortex reflects increased processing of reward drive that may translate into compulsive overeating. In contrast, bulimic subjects had greater activation of the insula and anterior cingulate compared with either binge eaters or controls (Schienle et al. 2009). Both the insula and anterior cingulate are involved in processing emotional stimuli, attention and response selection, and their activity correlates with autonomic arousal (Critchley et al., 2002; Phan et al., 2002). Increased activation of the insula and cingulate in bulimic subjects may reflect increased stress associated with a perceived loss of control over ingesting illicit foods. Another group reported that patients diagnosed with either anorexia nervosa or bulimia compared with healthy controls had greater activation of the ventral medial prefrontal cortex.
and anterior insula and reduced activation of the inferior parietal lobe and cerebellum in response to food pictures (Uher et al., 2003, 2004). Reduced activation of the inferior parietal lobe in anorexia nervosa patients in response to high calorie food images was confirmed (Santel et al., 2006). Brain activation in response to ‘thin words’ (celery, gaunt, salad, thin) or ‘fat words’ (huge, bacon, plump, burger) presented in a novel emotional Stroop task differed between anorexia nervosa patients (primarily purging-type) and healthy weight control subjects (Redgrave et al., 2008). Two clusters of activation (one at the junction of the insula, frontal and temporal lobes, and auditory cortex and a second containing voxels in the dorsolateral prefrontal cortex and dorsal anterior cingulate) in response to thin words were increased in patients compared with controls. In contrast, activation of the left dorsolateral prefrontal cortex and superior parietal lobe in response to fat words was decreased in patients relative to normal weight subjects. Reduced parietal activation may be related to a distorted body image since the parietal lobe has been implicated in integration of proprioception and visual information of self (Lou et al., 2004). Although responses in the various studies show some overlap, there are also differences. Differences may be attributed to differences in experimental protocol and differences in patient characteristics such as recovering versus non-recovering patients or binge-purging versus restrictive patients. These differences are exacerbated by the small number of reports to date.

Summary and conclusions

It is now recognized that ingestive behavior, once thought to be regulated principally by the hypothalamus, is modulated by a much broader neural network. An important component of this network is the mesocorticolimbic pathway which consists of the ventral tegmental area, nucleus accumbens, amygdala, hippocampus and prefrontal cortex. These brain regions comprise the neural substrates that both determine and respond to mood, pleasure, desire, experience and self recognition, and consequently, influence eating patterns that lead to the establishment of eating habits. In addition, our understanding of neuroendocrine control of eating has expanded to include corticolimbic brain structures. Reception and integration of peripheral signals of acute and chronic energy state leading to appropriate metabolic and ingestive responses are no longer limited to the hypothalamus. Rather, metabolic signals influence corticolimbic brain activity as a result of direct reception of homeostatic signals and indirect communication through the hypothalamus. This more encompassing view better integrates homeostatic and hedonic signals into a model of neuroendocrine control of food ingestion (Fig. 5).

Brain imaging studies reveal that food cues and metabolic signals activate the mesocorticolimbic neural network involved in processing reward. Activation is influenced by hunger and adiposity. Gender differences have been demonstrated despite having been studied infrequently. Gonadal steroids likely account for gender differences and for menstrual cycle dependent changes in ingestive behavior. Estrogen levels are highest in the periovulatory period and are unopposed by low progesterone concentrations. Increased dopamine signaling may occur during this ovarian steroid milieu as a result of estrogen stimulation of dopamine release and up-regulation of dopamine receptors. Sensitivity may be attenuated by increased progesterone secretion following ovulation and is maintained into the early follicular phase as a result of low estrogen levels. Heightened sensitivity to dopamine during the periovulatory period may lead to enhanced activation of the corticolimbic network. Our observation that food pictures activated the prefrontal cortex, orbitofrontal cortex, hippocampus and amygdala in the late follicular phase but not the luteal phase suggests that the responsiveness of this network to cues associated with reward is affected by ovarian steroids. Increased reward signaling in the periovulatory period may lead to smaller meals whereas reduced reward during the luteal phase may lead to larger meals and more binge eating. Although it may be counterintuitive that increased dopamine signaling would terminate a behavior, extracellular dopamine levels that exceed a threshold may be less rewarding and reduce wanting (Palmiter, 2007).

Many recent brain imaging studies have established that food and drug cues stimulate many of the same reward circuits. The evidence is summarized in Supplementary data, Table S1, and the reader is referred to several reviews for more on this important topic (Child-
Supplementary data are available at http://humupd.oxfordjournals.org/.

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**References**


Blaustein JD, Wade GN. Ovarian influences on the meal patterns of female rats. *Physiol Behav* 1976; **17**:201–208.


Farooqui IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, O’Rahilly S. Effects of


Huklhom CJ, van Dielen FM, Buurman WA, Westerterp-Plantenga MS, Campfield LA, Saris WH. The effect of pegylated recombinant human...


Reed SC, Levin FR, Evans SM. Changes in mood, cognitive performance and appetite in the late luteal and follicular phases of the menstrual cycle in women with and without PMDD (premenstrual dysphoric disorder). Horm Behav 2008;54:185–193.


