Central nervous system regulation of eating: insights from human brain imaging

Olivia M. Farr, Chiang-shan R. Li, Christos S. Mantzoros

PII: S0026-0495(16)00033-0
DOI: doi: 10.1016/j.metabol.2016.02.002
Reference: YMETA 53377

To appear in: *Metabolism*

Received date: 22 December 2015
Revised date: 30 January 2016
Accepted date: 1 February 2016

Please cite this article as: Farr Olivia M., Li Chiang-shan R., Mantzoros Christos S., Central nervous system regulation of eating: insights from human brain imaging, *Metabolism* (2016), doi: 10.1016/j.metabol.2016.02.002

Central Nervous System Regulation of Eating: Insights from Human Brain Imaging

Olivia M. Farr[1]*, Chiang-shan R. Li[2,3,4], Christos S. Mantzoros[1]

[1]Division of Endocrinology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA 02215
[2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06519
[3]Department of Neuroscience, Yale University School of Medicine, New Haven, CT 06520
[4]Interdepartmental Neuroscience Program, Yale University School of Medicine, New Haven, CT 06520

(Running title: food and the brain)

*Address correspondence to:

Olivia Farr, Ph.D.
Beth Israel Deaconess Medical Center
330 Brookline Ave, ST820
Boston, MA 02215

Phone: 617-667-8636
Email: ofarr@bidmc.harvard.edu

Disclosure Statement: The authors have nothing to disclose.

Funding: NIH 5T32HD052961

Abstract Word Count: 151
Text Word Count: 4,393
References: 202
Figures: 7

Abbreviations: CNS, central nervous system; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalogram; EEG, electroencephalogram; PET, positron emission tomography; D2, dopamine-2; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine- related transcript; AgRP, agouti-related protein; NPY, neuropeptide Y; VTA, ventral tegmental area; SN, substantia nigra; OFC, orbitofrontal cortex; pre-SMA, pre-supplementary motor area; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; AgRP, agouti-related peptide; ARC, arcuate nucleus; AVP, arginine-vasopressin; BDNF, brain-derived neurotrophic factor; CART, cocaine- and amphetamine regulated transcript; DMH, dorsomedial hypothalamus; LH, lateral hypothalamus; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY; TRH, thyroid-releasing hormone; VMH, ventromedial nucleus

Abstract

Appetite and body weight regulation are controlled by the central nervous system (CNS) in a rather complicated manner. The human brain plays a central role in integrating internal and external inputs to modulate energy homeostasis. Although homeostatic control by the hypothalamus is currently considered to be primarily responsible for controlling appetite, most of the available evidence derives from experiments in rodents, and the role of this system in regulating appetite in states of hunger/starvation and in the pathogenesis of overeating/obesity remains to be fully elucidated in humans. Further, cognitive and affective processes have been implicated in the dysregulation of eating behavior in humans, and their exact relative contributions as well as the respective underlying mechanisms remain unclear. We briefly review each of these systems here and present the current state of research in an attempt to update clinicians and clinical researchers alike on the status and future directions of obesity research.

Obesity is an increasing concern worldwide and was declared a global health epidemic in 2003 by the World Health Organization. Particularly pronounced in industrialized countries including the United States, a third or more of the population presents with obesity and an additional third is overweight [1]. Other nations are rapidly following with a lag phase that reflects their degree of westernization. In order to understand and develop effective therapeutics for this medical condition, it is necessary to understand the central nervous system (CNS) mechanisms underlying eating behaviors and how these mechanisms become dysregulated.

Current research indicates that the brain circuitry which controls eating in humans is regulated not only by homeostatic mechanisms, but also by the reward, emotion/memory, attention, and cognitive control systems (**Figure 1**). These circuits interact to control energy intake and expenditure. Here, after introducing the techniques that are employed to study the human brain, we will describe each of these systems, beginning with the homeostatic control of eating in the hypothalamus and ending with the prefrontal processes of cognitive control.

Techniques to study the CNS in clinical research

The most commonly used techniques to examine the appetitive processes in human brains include neurocognitive testing and functional magnetic resonance imaging (fMRI). Neurocognitive testing can be described simply as targeted computer games which aim to capture a certain mental skill through a specific task. By simplifying real world experiences into these tasks, researchers obtain outcome measures of each of the cognitive components described above. For instance, the stop signal task or go/no-go task is often used to measure cognitive or inhibitory control [2-4] and can be combined with fMRI to study these complex mechanisms in the brain. Previous studies have found longer stop signal reaction times (SSRTs), which

represent poorer inhibitory control, to correlate with future weight gain [5]. Intensive lifestyle changes decrease SSRTs, representing improved inhibitory control, in adolescents [6]. However, neurocognitive testing alone is limited in scope. While specific outcome measures may provide basic information about cognitive performance/state, they do not describe how different brain areas or networks are involved or may be altered in disease states. These neural phenotypes can be captured when neurocognitive tasks are combined with fMRI. For example, even though there may be no difference in performance on neurocognitive tasks, obese and lean individuals display different patterns of brain activations to the same challenges during fMRI [4, 7-10]. These findings suggest that activations of specific brain areas may be altered or act to compensate in order to maintain neurocognitive performance. These changes in brain activations are related to real-life decisions in eating. For example, despite no difference on the cognitive control-related Stroop task, obese as compared to lean participants showed greater activation of the frontal cortex including the insula during incongruent stimuli, and this was related to reported binge eating [9].

Neuronal activations require an increased supply of oxygenated blood. FMRI relies on the differences in the magnetic properties of the oxygenated versus deoxygenated hemoglobins to create an image of the brain and detects functional activation by observing shifts in the magnetic signals. Thus, this represents an indirect measure of neural activity, which assumes that recently active brain areas use more oxygen. FMRI captures brain activity in the cortex with good spatial and acceptable temporal resolution but is susceptible, by nature, to artifacts from the sinuses, throat, and eyes. It is thus difficult to identify activity in some areas of interest to obesity research, including the hypothalamus [11] and orbitofrontal cortex [12]. Nonetheless, fMRI is considered to be one of the best tools currently available for the detection of regional brain

activations to specific cues or tasks. As mentioned earlier, fMRI is frequently conducted in conjunction with a behavioral task. In terms of studying the control of eating, the most common paradigms involve the presentation of food images or food delivery (such as giving a milkshake). For instance, brain responses to viewing food images have been repeatedly shown to be different between obese and lean individuals in the reward, emotional and cognitive control circuits [13-18]. Oral food presentation has also been observed to modulate brain activity in these circuits [19, 20]. FMRI can be expanded to study not only the activation of the human brain but also how these brain centers are related and communicate with each other. Functional connectivity, which assesses temporal relationships between regional activities, can be computed to characterize how individual brain regions communicate to subserve responses to viewing of food images or food intake. For instance, participants reporting high chronic stress have greater connectivity between the amygdala and putamen but less connectivity between the amygdala and anterior cingulate and prefrontal cortex while viewing high calorie food cues as compared to participants with low stress exposures that may underlie food consumption during stress [21].

FMRI can also be conducted with participants resting – i.e., not performing any behavioral tasks. The so-called resting state fMRI provides data to query brain connectivity, which numerous investigations over the last decade have shown to mirror anatomic connections [22, 23]. In fact, by examining how individual voxels of the brain are connected to one another, researchers have also employed various analytical tools to identify or refine the networks of brain regions that function in a concerted manner [24-26]. For instance, functional connectivity of the insula during the resting state has been observed to differ between pre- and post-prandial states, where connectivity between insula and frontal cortex were stronger in the fasting state but connections between insula and default mode areas were stronger in the satiated state [27].These

connectivity studies are frequently complemented with a different MR imaging technique called Diffusion Tensor Imaging (DTI) to characterize structural (white-matter) connectivities and to quantify the integrity of these connectivities between brain regions. For example, a recent study found changes in DTI and resting-state functional connectivity in obese individuals amongst areas involved in reward, emotion, and memory [28]. Another study used DTI to observe changes in white matter tracts connecting the prefrontal (cognitive control) and limbic (emotion and reward) cortices, potentially indicating a mechanism for cognitive decline in obesity [29]. In summary, MRI is a multi-faceted tool which can provide both structural and functional information about the brain.

Magnetoencephalogram (MEG) and Electroencephalogram (EEG) are non-invasive tools which detect brain activation with better temporal resolution but worse spatial resolution than fMRI. Neural activity is composed of changes in electrical currents, and EEGs detect the electrical potentials directly and MEGs detect the magnetic fields generated by the electrical currents. MEGs have slightly better spatial resolution than EEGs, but both are inferior to fMRI. Analytical tools are available to reconstruct the loci of activation based on the spatial distribution of MEG and EEG signals and facilitate comparisons of MEG/EEG and fMRI findings [30]. In obesity research, MEG has been used to determine the temporal profile of the neural response to categorizing and memorizing food cues [31]. EEG has been utilized to examine differences in responses to emotional or food cues in obesity [32] and how the overall brain response to food cues differ before and after exercise in obese individuals [33]. For instance, frontal beta activity recorded by EEG during an attention task correlated with loss of control over eating measures in adolescent girls, indicating links between frontal activations, attention, and food intake that may underlie the development of obesity [34].

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging employ radioactive tracers to examine where specific target molecules, including neurotransmitter receptors and transporters, are located in the brain and how the binding potentials of these molecular targets are altered in a neuropsychiatric condition. PET and SPECT have poor temporal resolution, acceptable spatial resolution, and are considered invasive due to the injection of a radioligand and need of an arterial line. Unlike fMRI, PET and SPECT are largely used to demonstrate quantitatively how and where specific molecules exert their actions in the brain. For instance, PET studies have consistently observed that obese individuals have lower dopamine-2 (D2) receptor availability in the striatum than lean individuals (for a review, see Val-Laillet *et al.* [17]). A recent study showed that the binding potentials of norepinephrine transports are decreased in the thalamus in obese as compared to non-obese individuals [35]. PET imaging has also shown that energy balance and weight loss is related to CNS receptor occupancy of the cannabinoid receptors, which are known to regulate mood and memory in addition to appetite [36]. While PET imaging is mostly used to identify the locations of actions of specific molecules or receptors, imaging with fluorodeoxyglucose can be used to measure glucose metabolism as an indirect index of cerebral activity.

Homeostatic brain systems

Control of eating in the human brain is complicated and involves several neural systems. The homeostatic control of eating primarily involved the hypothalamus in regulating food intake. The arcuate nucleus of the hypothalamus controls appetite and contains neurons which express pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which decrease appetite and increase energy expenditure, and neurons which express agouti-related protein (AgRP) and neuropeptide Y (NPY), which increase appetite and decrease energy

expenditure [37]. These neurons are modulated by peripheral hormonal signals, which act in the hypothalamus to inhibit or excite these neurons to alter appetite. The neurons in the arcuate nucleus communicate with other orexigenic and anorexigenic neurons in other nuclei of the hypothalamus to control eating (**Figure 2**; [38-40]).

Leptin is one such molecule secreted in the periphery by adipose tissue, circulating at levels proportional to the amount of body fat and in response to acute changes in energy intake. The primary role of leptin is to signal the amount of stored energy as adipose tissue and regulate energy intake and expenditure [40-42]. Severe caloric restriction for two days results in a 50% decrease and for three days results in a 90% decrease from baseline in circulating leptin, indicating a secondary role for leptin to signal acute food deprivation [43]. At higher levels of body fat, leptin circulates at higher levels and in physiological conditions, inhibits food intake and increases energy expenditure by inhibiting AgRP/NPY neurons and stimulating POMC/CART neurons in the hypothalamus. Conversely, at lower levels of body fat, leptin circulates at lower levels and increases food intake and decreases energy expenditure. In neurotypical individuals, this mechanism serves to maintain body weight and energy homeostasis. In obesity, high levels of adipose tissue result in high levels of circulating leptin for a prolonged period of time, and leptin resistance or tolerance forms, disrupting this homeostatic mechanism [44-46]. Several other molecules produced in the periphery provide feedback to the hypothalamus to regulate energy intake and expenditure. For instance, ghrelin, which is produced in the gastrointestinal tract, increases food intake and decreases energy expenditure and becomes dysregulated in obesity [47]. Other key peripheral molecules impacting the hypothalamus and energy homeostasis include insulin and amylin, which are secreted by the pancreas, adiponectin, which is secreted by adipose tissue, and irisin, which is secreted by

muscle, and are all affected by obesity [48-64]. Glucagon-like peptide-1 (GLP-1) is a relatively newly discovered molecule secreted by the gut and acting in the brain to decrease appetite and cause weight loss [65-69]. GLP-1 analogs have recently been approved to treat obesity for this reason [70-72]. Stimulation of the hypothalamus has been observed to modulate eating behaviors in rodents. For instance, in several classical experiments, stimulation of the lateral nucleus of the hypothalamus increased food intake and body weight [73-75]. More recently, deep brain stimulation of this area in rats demonstrated the opposite effect [76]. Most studies have shown that stimulation of the ventromedial hypothalamus causes a decrease in food intake and body weight in rodents [77-79]. Increased food intake was observed with stimulation of the ventromedial hypothalamus in monkeys [80]. This discrepancy highlights the potential differences between rodents and humans in the role of the hypothalamus and its subnuclei in regulating eating behavior. Humans appear to involve a much more complicated brain network in controlling eating and appetite. That is, although dysregulated homeostatic control of eating may contribute to obesity, this mechanism may not capture the larger picture of cognitive and affective circuitry implicated in dysregulated eating in humans.

Limited evidence has been demonstrated in humans for the role of the hypothalamus in the regulation of appetite and eating. Activation of the hypothalamus as well as the thalamus, midbrain, and striatum, to a milkshake predicted weight gain within a year in a fMRI study of humans [81]. The hypothalamus receives external signals and communicates directly with components of the reward and emotion and memory systems, as well as through the thalamus to the cognitive control and other cortical areas (**Figure 3**), and thus, activation of the hypothalamus may be subject to control/influence by these higher systems in humans. That is,

although the hypothalamus is critical to homeostatic control of eating, it is likely to be influenced by multiple component systems to determine food intake.

As obese individuals consume food at levels above homeostatic maintenance, these other regulatory systems may exert more control over the drive to eat as dictated by the hypothalamus. Thus, there is a need for more translational research to understand how the hypothalamic mechanisms may be impacted in obesity as a result of "supra-homeostatic" control. Further, new imaging and analytical tools to capture the actions of the hypothalamus with better resolution and accuracy in humans will be an asset to obesity research.

Reward systems

Several researchers have hypothesized that altered reward signaling in the brain is the root cause of obesity [14, 20, 82-100]. Food is naturally rewarding and typically acts on the reward pathways in the brain. These pathways consist of dopaminergic neurons which originate in the ventral tegmental area (VTA) and substantia nigra (SN) in the midbrain and project throughout the human brain. The nucleus accumbens, striatum, and orbitofrontal cortex (OFC) are key areas involved in receiving and integrating these dopaminergic signals for actions (**Figure 4**). Indeed, these areas have been found to respond to both viewing of food cues and consumption of food during fMRI in humans [14, 84, 85, 96, 97, 100].

There are two main theories regarding how the reward networks may be altered in obesity (**Figure 5**). In one theory, hyporesponsivity to rewards in leads individuals to seek and consume more high calorie and high fat foods and to become obese. PET studies have consistently reported lower availability of dopamine 2 (D2) receptors in the striatum in obese as compared to normal weight individuals [101-105]. Lower D2 receptor availability in rats also correlated with

greater weight gain over time [106] and similar results have been observed in humans [107]. Altogether, these findings suggest that lower dopaminergic signaling may lead certain individuals to seek highly rewarding (high calorie or high fat) foods and this in turn leads to obesity. On the other hand, there is evidence that exposure to high fat or high calorie foods may lead to a decreased reward state. When rats were exposed to a high calorie diet, they had higher weight, lower D2 receptor levels, and higher reward thresholds, as compared to those exposed to a regular diet [108]. The hypothesized association between a under-responsive reward circuit and habitual food intake have underlined much of the discussion likening high fat or calorie foods to drugs of addiction [14, 82, 90, 95, 96, 98].

In the other theory, exposure to highly rewarding foods results in hyper-responsivity to food cues, which leads individuals to seek foods more often and in greater quantity. With increased exposure to these highly rewarding foods, there is a larger disconnect between reward response to food cues and response to consuming foods, which leads them to eat more foods to achieve the expected reward. This theory is supported by findings of increased activation of the nucleus accumbens, midbrain, and OFC in obesity to visual food cues [109-113] and anticipation of milkshake [114]. Although obese individuals may have also found food consumption rewarding, increased exposure to high fat or calorie foods decreases the response of the reward system to food consumption but not to food cues. In support are findings in mice that continued ingestion of glucose decreases the dopaminergic response in the brain [115]. These two non-exclusive hypotheses are difficult to test in humans, as most humans have already been exposed, life-long, to high fat or calorie foods. However, both theories posit a role of the reward systems in dysregulated appetite and obesity. Future long-term observational and interventional studies

are needed to fully explore how reward function and dysfunction are associated with dysfunctional eating and obesity.

Emotion/memory systems

Clinically, emotions are well-known to be potent modulators of appetite. Depression and anxiety are common comorbidities of obesity, and depressed mood is related to central obesity and poorer diet quality [116-120]. Regarding shorter-term emotions, joy and anger both increase appetite and create poorer dietary choices as compared to fear and sadness [121]. Furthermore, these effects are more pronounced in women than in men [121]. Some investigators suggest that obese individuals may alter eating behavior in order to regulate their emotions and/or that obese individuals fail to recognize internal cues of hunger and thus cannot regulate their eating appropriately [122]. Stress is also known to cause changes in appetite as well as predispose individuals to obesity and cardiometabolic risk (for a recent discussion, see Farr *et al.* [123]).

The amygdala is the primary brain area regulating appetite with response to emotions. Indeed, the amygdala activates to food cues [124, 125], and this response is increased in childhood, adolescent, and adult obesity [126-129]. Activation of the amygdala also predicts consumption of high fat or high calorie foods [130]. Participants who had greater response of the amygdala to food cues when not hungry were more likely to gain weight [131]. These participants also displayed an increased functional connectivity between the amygdala to the hypothalamus during satiety to food cues, which suggests that the amygdala may mediate a hunger response even when an individual is not physically hungry [131]. Higher levels of circulating leptin in adolescents correlated with activation of the amygdala to high calorie food cues [129]. The stress relieving effect induced by sucrose has been found to be mediated through

an amygdala circuit which communicates to the hypothalamic-pituitary-adrenal axis [132]. Together, evidence abounds that the amygdala is involved in emotional eating and future work may elucidate how amygdala regulates appetite and eating through its connectivity to the hypothalamus and the molecular determinants of the underlying mechanisms.

Memory, largely regulated by the hippocampus and parahippocampal formation, may also play a role in dysfunctional eating behaviors. It has been hypothesized that decreased functioning of the hippocampus leads to increased food intake and poorer dietary quality in turn leading to obesity [133, 134] (**Figure 6**). Although typical meal timing can be controlled by circadian rhythms and the suprachiasmatic nucleus, there is much evidence that this system is frequently overridden by memory and experiences [134]. Indeed, both sated rodents and humans will eat with cues or context for highly palatable foods, overriding the typical mechanisms for eating [135-139]. The hippocampus receives input regarding food cues from many other areas including the insula, orbitofrontal cortex, and arcuate nucleus of the hypothalamus [140-143]. Additionally, the hippocampus is influenced by peripheral mechanisms such as leptin and ghrelin to regulate food intake [144-147]. Hippocampal lesions cause increased food intake and subsequent obesity in rodents [148]. Similarly, humans with hippocampal lesions cannot remember if they are hungry, will not remember having eaten and will eat again, even when they had just eaten until full [149-151]. Research also demonstrates that diet-induced obesity impairs hippocampal functions [152-155]. Obesity could compromise hippocampal functioning through increased blood-brain barrier permeability allowing inflammatory cytokines to enter the brain [154, 156], inflammatory processes within the CNS [157, 158], and/or fatty liver inflammatory signals [153, 159]. While altered cytokine signaling in the inflammatory state of obesity may be partially to blame for compromised CNS centers [160-162], tight junctions of the blood-brain

barrier likely prevent cytokines from entering most areas of the brain [163]. However, since parts of the hypothalamus are unprotected by the blood-brain barrier, they may still enter and have effects there. Regardless, the hippocampus is protected by the blood-brain barrier, and there is evidence that inflammation in the CNS may be carried out by microglia [164, 165]. In states of obesity, microglial action has been observed to impair hippocampal function through these CNS inflammatory processes [166, 167]. Altogether, the evidence suggests that obesity impairs hippocampal function, likely through inflammatory processes, which in turn causes obesity, leading to a vicious cycle of dysfunctional eating (**Figure 6**). Thus, there appears to be a clear relationship between memory/hippocampal function and obesity. Extant studies suggest that this may be more potent a relationship in rodents than humans, and future work is warranted to explore the links between memory and eating behaviors in humans, as moderated by other cognitive and affective processes.

Attention systems

Attention to foods and food cues has been repeatedly implicated in obesity, where obese individuals attend more to food cues and normal weight individuals who pay more attention to food cues display patterns of overeating and weight gain [168-170]. Indeed, individuals tend to pay more attention to things which they value, as these items have more salience or importance to that individual. While there is a general pattern of obese individuals attending more to food cues, it is not a blanket rule, and subcategories of obese individuals demonstrate more attentional bias than others, including those showing high external eating or eating to food cues despite internal cues of satiety [171-173]. In eye tracking studies, individuals demonstrate an attentional bias to high calorie or high fat food cues regardless of their weight during fasting, although obese

but not normal weight participants maintain this attentional bias while in the fed state [174]. Altogether, there appears to be attention-related modulation of brain activity to food cues, and higher attention to food cues leads to food consumption and weight gain.

The brain network for attention has been well-defined and includes the parietal and visual cortices as well as some areas of the frontal cortex [175, 176]. In fMRI studies with humans, increased activation in the occipital cortex has been demonstrated for high calorie or high fat food images, suggesting increased attention to these stimuli [177, 178]. Parietal cortex has been observed to activate during "appetite control" (imagined restraint from eating) in humans [179]. In another study, as participants were trained to select less subjectively valued or desired food images, they demonstrated decreased activation in the parietal cortices [180], suggesting a change in attention with training. Adolescents display increased activation of the parietal and occipital cortices when viewing food as compared to non-food commercials, suggesting an attentional bias [181]. Normal weight individuals who are prone to becoming obese, as defined by family history and eating habits, display greater parietal and occipital activation to food cues in the fed state [182]. Greater activation of the parietal and occipital cortices to food cues predicted less weight lost during dieting, suggesting that more attention to food cues may prohibit weight loss success [183]. Another study demonstrated similar effects with greater attention-related parietal activity to food cues predicting higher BMI and future weight gain [113]. Altogether, there is strong evidence that altered attention in parietal and occipital cortices to food and food cues leads to higher weight and resistance to losing weight.

Cognitive control systems

Cognitive control consists of executive functions including the inhibition of prepotent responses. In terms of eating, cognitive control allows individuals to refuse a piece of cake when they are hungry, knowing that this would not be the healthiest choice. The prefrontal cortex composes much of the cognitive control network, particularly the cingulate cortex, inferior frontal cortex, pre-supplementary motor area (pre-SMA) and dorsolateral prefrontal cortex (DLPFC) [184]. Several studies have demonstrated impaired inhibitory control in obese humans and a link of impaired control to future weight gain in normal weight individuals [4, 5, 179, 185-195]. Poorer inhibitory control, even on non-food-related tasks, has been observed to correlate with high calorie food intake [5] and a resistance to losing weight [195]. In normal weight participants, the use of transcranial magnetic stimulation to deactivate the DLPFC has caused decreased valuation of food cues [196], suggesting that this area makes valuations about food choices. Increased DLPFC activation was observed when participants displayed self-restraint in unhealthy food choices, suggesting again that the DLPFC may evaluate food choices [197]. When asked to imagine inhibiting themselves from eating foods while looking at food images, individuals activated areas of the cognitive control network, including the cingulate cortex, pre-SMA, and DLPFC [179]. Investigators have theorized that impaired cognitive control may unleash increased reward responses to food cues and thus overeating [198, 199] (**Figure 7**). Obese individuals have less metabolism as measured by PET imaging, or decreased activity, in the prefrontal cortex and this change correlates with dopamine receptor availability and BMI [104, 200]. Across ages, higher weight has been associated with less gray matter in the prefrontal cortex, which has been suggested to lead to the cognitive deficits, as observed in dementia, seen

more frequently with obesity [201]. When participants lose weight, there is evidence of improved executive function [202]. Altogether, obese individuals demonstrate deficits in cognitive control both in general and food-specific tasks. On the other hand, it remains unclear whether poor cognitive or inhibitory control may be caused by obesity or causes obesity.

Conclusions

The control of eating in the human brain is complicated, involving several cortical and subcortical systems and a multitude of cognitive and affective processes. Experiments in rodents have provided critical insights into the neural circuits regulating appetite and eating behavior. However, these animal studies may only capture some of the complexity involved in dysfunctional eating in humans. FMRI combined with neurocognitive testing and food cue paradigms in humans hold great promise in unraveling how the homeostatic, reward, cognitive and affective systems interact to control appetite and eating. PET and SPECT imaging are instrumental to revealing the molecular determinants of these neural processes. Together, these imaging tools are critical to understanding how the brain is altered in obesity including potential subtypes of obesity (e.g. emotional eaters) and to developing new pharmacological regimens to effectively treat obesity.

Acknowledgments

Olivia M. Farr is supported by a NICHD 5T32HD052961.

Conflicts of Interest

The authors have no conflicts to disclose.

Contributions

OMF, CSRL, and CSM wrote the manuscript.

Figure 1. Control of eating in human brain is controlled by homeostatic brain systems (hypothalamus), attention systems (including the parietal and visual cortices), emotion and memory systems (such as the amygdala and hippocampus), cognitive control (including the prefrontal cortex), and the reward network (including the VTA and striatum).

Figure 2. Schematic of nuclei in the hypothalamus which contribute to the control of eating as well as inputs from the periphery. The arcuate (ARC) nucleus contains NPY/AgRP neurons which are orexigenic and POMC/CART neurons which are anorexigenic. These neurons communicate with the other nuclei and neurons which release other orexigenic or anorexigenic peptides. Please note that the neurons may not release all anorexigenic or orexigenic peptides shown (e.g. a single neuron may not release TRH, Oxytocin, AVP and CART in the PVN), but are shown in groups by whether they are anorexigenic or orexigenic in each nucleus. AgRP, agouti-related peptide; ARC, arcuate nucleus; AVP, arginine-vasopressin; BDNF, brain-derived neurotrophic factor; CART, cocaine- and amphetamine regulated transcript; DMH, dorsomedial hypothalamus; LH, lateral hypothalamus; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY; TRH, thyroid-releasing hormone; VMH, ventromedial nucleus.

Figure 3. General map of connectivity of the hypothalamus to other CNS centers important for energy intake. These areas communicate with each other and the hypothalamus to control energy intake. Importantly, the hypothalamus also receives key inputs from the periphery regarding

available energy (recent intake and storage). NAcc, nucleus accumbens; OFC, orbitofrontal cortex; SN, substantia nigra; VTA, ventral tegmental area.

Figure 4. The reward system mainly consists of the dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra (SN) to the orbitofrontal cortex (OFC) and striatum, particularly the Nucleus Accumbens (NAcc).

Figure 5. Theories of how reward responsivity is affected in obesity: hyperresponsivity (**a**) and hyporesponsivity (**b**). The first theory suggests that obese individuals have a heightened reward response to food cues but after increased food consumption, this leads to a decreased response to reward to actual food consumption (but not food cues), and this disconnect leads to greater food intake over time. The second theory posits that individuals with a natural hyposensitivity for rewards consume more food because they require more food consumption and more high calorie or high fat foods to achieve the same level of reward.

Figure 6. Memory influences eating behaviors in a cyclical manner. Decreased hippocampal activity leads to decreased memory of meals and increased response to food cues. This leads to increased caloric consumption and obesity, which in turn leads to increased inflammation and cardiometabolic dysfunction which in turn decreases hippocampal function.

Figure 7. A theory of how cognitive control may interact with reward and food consumption is that in typical cases, heightened cognitive control may decrease the reward system's activation to food cues and thus decrease food consumption (**a**). This may be altered in obesity, where cognitive control is impaired, and the reward system may be heightened, leading to increased food consumption (**b**).

References

1 Johnelle Sparks P, Bollinger M. A demographic profile of obesity in the adult and veteran us populations in 2008. *Population Res Policy Rev* 2011;13: 211-33.
2 Batterink L, Yokum S, Stice E. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: An fmri study. *Neuroimage* 2010;52(4): 1696-703.
3 Hendrick OM, Ide JS, Luo X, Li CS. Dissociable processes of cognitive control during error and non-error conflicts: A study of the stop signal task. *PLoS One* 2010;5(10): e13155.
4 Hendrick OM, Luo X, Zhang S, Li CS. Saliency processing and obesity: A preliminary imaging study of the stop signal task. *Obesity (Silver Spring)* 2012;20(9): 1796-802.
5 Levitan RD, Rivera J, Silveira PP, Steiner M, Gaudreau H, Hamilton J, et al. Gender differences in the association between stop-signal reaction times, body mass indices and/or spontaneous food intake in pre-school children: An early model of compromised inhibitory control and obesity. *Int J Obes (Lond)* 2015;39(4): 614-9.
6 Kulendran M, Vlaev I, Sugden C, King D, Ashrafian H, Gately P, et al. Neuropsychological assessment as a predictor of weight loss in obese adolescents. *Int J Obes (Lond)* 2014;38(4): 507-12.
7 Stoeckel LE, Murdaugh DL, Cox JE, Cook EW, 3rd, Weller RE. Greater impulsivity is associated with decreased brain activation in obese women during a delay discounting task. *Brain Imaging Behav* 2013;7(2): 116-28.
8 Krafft CE, Schwarz NF, Chi L, Weinberger AL, Schaeffer DJ, Pierce JE, et al. An 8-month randomized controlled exercise trial alters brain activation during cognitive tasks in overweight children. *Obesity (Silver Spring)* 2014;22(1): 232-42.
9 Balodis IM, Molina ND, Kober H, Worhunsky PD, White MA, Rajita S, et al. Divergent neural substrates of inhibitory control in binge eating disorder relative to other manifestations of obesity. *Obesity (Silver Spring)* 2013;21(2): 367-77.
10 Moreno-Lopez L, Soriano-Mas C, Delgado-Rico E, Rio-Valle JS, Verdejo-Garcia A. Brain structural correlates of reward sensitivity and impulsivity in adolescents with normal and excess weight. *PLoS One* 2012;7(11): e49185.
11 Salem V, Dhillo WS. Imaging in endocrinology: The use of functional mri to study the endocrinology of appetite. *Eur J Endocrinol* 2015.
12 Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: Current knowledge and future directions. *Obes Rev* 2012;13(1): 43-56.
13 Behary P, Miras AD. Brain responses to food and weight loss. *Exp Physiol* 2014;99(9): 1121-7.
14 Garcia-Garcia I, Horstmann A, Jurado MA, Garolera M, Chaudhry SJ, Margulies DS, et al. Reward processing in obesity, substance addiction and non-substance addiction. *Obes Rev* 2014;15(11): 853-69.
15 Machann J, Horstmann A, Born M, Hesse S, Hirsch FW. Diagnostic imaging in obesity. *Best Pract Res Clin Endocrinol Metab* 2013;27(2): 261-77.
16 Pursey KM, Stanwell P, Callister RJ, Brain K, Collins CE, Burrows TL. Neural responses to visual food cues according to weight status: A systematic review of functional magnetic resonance imaging studies. *Front Nutr* 2014;1: 7.
17 Val-Laillet D, Aarts E, Weber B, Ferrari M, Quaresima V, Stoeckel LE, et al. Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. *Neuroimage Clin* 2015;8: 1-31.

18 Connolly L, Coveleskie K, Kilpatrick LA, Labus JS, Ebrat B, Stains J, et al. Differences in brain responses between lean and obese women to a sweetened drink. *Neurogastroenterol Motil* 2013;25(7): 579-e460.
19 Rudenga KJ, Sinha R, Small DM. Acute stress potentiates brain response to milkshake as a function of body weight and chronic stress. *Int J Obes (Lond)* 2013;37(2): 309-16.
20 Small DM. Individual differences in the neurophysiology of reward and the obesity epidemic. *Int J Obes (Lond)* 2009;33 Suppl 2: S44-8.
21 Tryon MS, Carter CS, Decant R, Laugero KD. Chronic stress exposure may affect the brain's response to high calorie food cues and predispose to obesogenic eating habits. *Physiol Behav* 2013;120: 233-42.
22 Li CS, Ide JS, Zhang S, Hu S, Chao HH, Zaborszky L. Resting state functional connectivity of the basal nucleus of meynert in humans: In comparison to the ventral striatum and the effects of age. *Neuroimage* 2014;97: 321-32.
23 Zhang S, Hu S, Chao HH, Li CR. Resting-state functional connectivity of the locus coeruleus in humans: In comparison with the ventral tegmental area/substantia nigra pars compacta and the effects of age. *Cereb Cortex* 2015.
24 Zhang S, Li CS. Functional connectivity mapping of the human precuneus by resting state fmri. *Neuroimage* 2012;59(4): 3548-62.
25 Zhang S, Li CS. Functional clustering of the human inferior parietal lobule by whole-brain connectivity mapping of resting-state functional magnetic resonance imaging signals. *Brain Connect* 2014;4(1): 53-69.
26 Zhang S, Ide JS, Li CS. Resting-state functional connectivity of the medial superior frontal cortex. *Cereb Cortex* 2012;22(1): 99-111.
27 Wright H, Li X, Fallon NB, Crookall R, Giesbrecht T, Thomas A, et al. Differential effects of hunger and satiety on insular cortex and hypothalamic functional connectivity. *Eur J Neurosci* 2016.
28 Park BY, Seo J, Yi J, Park H. Structural and functional brain connectivity of people with obesity and prediction of body mass index using connectivity. *PLoS One* 2015;10(11): e0141376.
29 Kullmann S, Callaghan MF, Heni M, Weiskopf N, Scheffler K, Haring HU, et al. Specific white matter tissue microstructure changes associated with obesity. *Neuroimage* 2015;125: 36-44.
30 Chang A, Chen CC, Li HH, Li CS. Perigenual anterior cingulate event-related potential precedes stop signal errors. *Neuroimage* 2015;111: 179-85.
31 Stingl KT, Rogic M, Stingl K, Canova C, Tschritter O, Braun C, et al. The temporal sequence of magnetic brain activity for food categorization and memorization--an exploratory study. *Neuroimage* 2010;52(4): 1584-91.
32 Versace F, Kypriotakis G, Basen-Engquist K, Schembre SM. Heterogeneity in brain reactivity to pleasant and food cues: Evidence of sign-tracking in humans. *Soc Cogn Affect Neurosci* 2015.
33 Fearnbach SN, Silvert L, Keller KL, Genin PM, Morio B, Pereira B, et al. Reduced neural response to food cues following exercise is accompanied by decreased energy intake in obese adolescents. *Int J Obes (Lond)* 2015.
34 Bauer LO, Manning KJ. Challenges in the detection of working memory and attention decrements among overweight adolescent girls. *Neuropsychobiology* 2016;73(1): 43-51.

35 Li CS, Potenza MN, Lee DE, Planeta B, Gallezot JD, Labaree D, et al. Decreased norepinephrine transporter availability in obesity: Positron emission tomography imaging with (s,s)-[(11)c]o-methylreboxetine. *Neuroimage* 2014;86: 306-10.
36 Addy C, Wright H, Van Laere K, Gantz I, Erondu N, Musser BJ, et al. The acyclic cb1r inverse agonist taranabant mediates weight loss by increasing energy expenditure and decreasing caloric intake. *Cell Metab* 2008;7(1): 68-78.
37 Schwartz MW, Porte D, Jr. Diabetes, obesity, and the brain. *Science* 2005;307(5708): 375-9.
38 Chan JL, Mantzoros CS. Leptin and the hypothalamic-pituitary regulation of the gonadotropin-gonadal axis. *Pituitary* 2001;4(1-2): 87-92.
39 Mantzoros CS. The role of leptin and hypothalamic neuropeptides in energy homeostasis: Update on leptin in obesity. *Growth Horm IGF Res* 2001;11 Suppl A: S85-9.
40 Stieg MR, Sievers C, Farr O, Stalla GK, Mantzoros CS. Leptin: A hormone linking activation of neuroendocrine axes with neuropathology. *Psychoneuroendocrinology* 2015;51: 47-57.
41 Farr OM, Gavrieli A, Mantzoros CS. Leptin applications in 2015: What have we learned about leptin and obesity? *Curr Opin Endocrinol Diabetes Obes* 2015;22(5): 353-9.
42 Farr OM, Tsoukas MA, Mantzoros CS. Leptin and the brain: Influences on brain development, cognitive functioning and psychiatric disorders. *Metabolism* 2015;64(1): 114-30.
43 Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. *J Clin Invest* 2003;111(9): 1409-21.
44 Balland E, Cowley MA. New insights in leptin resistance mechanisms in mice. *Front Neuroendocrinol* 2015.
45 Crujeiras AB, Carreira MC, Cabia B, Andrade S, Amil M, Casanueva FF. Leptin resistance in obesity: An epigenetic landscape. *Life Sci* 2015;140: 57-63.
46 Sainz N, Barrenetxe J, Moreno-Aliaga MJ, Martinez JA. Leptin resistance and diet-induced obesity: Central and peripheral actions of leptin. *Metabolism* 2015;64(1): 35-46.
47 Zigman JM, Bouret SG, Andrews ZB. Obesity impairs the action of the neuroendocrine ghrelin system. *Trends Endocrinol Metab* 2015.
48 Bluher M, Mantzoros CS. From leptin to other adipokines in health and disease: Facts and expectations at the beginning of the 21st century. *Metabolism* 2015;64(1): 131-45.
49 Polyzos SA, Toulis KA, Goulis DG, Zavos C, Kountouras J. Serum total adiponectin in nonalcoholic fatty liver disease: A systematic review and meta-analysis. *Metabolism* 2011;60(3): 313-26.
50 Van de Voorde J, Pauwels B, Boydens C, Decaluwe K. Adipocytokines in relation to cardiovascular disease. *Metabolism* 2013;62(11): 1513-21.
51 Wu ZJ, Cheng YJ, Gu WJ, Aung LH. Adiponectin is associated with increased mortality in patients with already established cardiovascular disease: A systematic review and meta-analysis. *Metabolism* 2014;63(9): 1157-66.
52 Aroor AR, McKarns S, Demarco VG, Jia G, Sowers JR. Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance. *Metabolism* 2013;62(11): 1543-52.
53 Bjorntorp P. Endocrine abnormalities of obesity. *Metabolism* 1995;44(9 Suppl 3): 21-3.
54 Deer J, Koska J, Ozias M, Reaven P. Dietary models of insulin resistance. *Metabolism* 2015;64(2): 163-71.

55 Gerich JE. Metabolic abnormalities in impaired glucose tolerance. *Metabolism* 1997;46(12 Suppl 1): 40-3.
56 Seretis K, Goulis DG, Koliakos G, Demiri E. The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: A systematic review and meta-analysis. *Metabolism* 2015;64(12): 1640-9.
57 Tsatsoulis A, Mantzaris MD, Bellou S, Andrikoula M. Insulin resistance: An adaptive mechanism becomes maladaptive in the current environment - an evolutionary perspective. *Metabolism* 2013;62(5): 622-33.
58 Wabitsch M, Hauner H, Heinze E, Teller WM. The role of growth hormone/insulin-like growth factors in adipocyte differentiation. *Metabolism* 1995;44(10 Suppl 4): 45-9.
59 Walker M. Obesity, insulin resistance, and its link to non-insulin-dependent diabetes mellitus. *Metabolism* 1995;44(9 Suppl 3): 18-20.
60 Bostrom PA, Fernandez-Real JM, Mantzoros C. Irisin in humans: Recent advances and questions for future research. *Metabolism* 2014;63(2): 178-80.
61 Crujeiras AB, Zulet MA, Lopez-Legarrea P, de la Iglesia R, Pardo M, Carreira MC, et al. Association between circulating irisin levels and the promotion of insulin resistance during the weight maintenance period after a dietary weight-lowering program in obese patients. *Metabolism* 2014;63(4): 520-31.
62 Polyzos SA, Kountouras J, Anastasilakis AD, Geladari EV, Mantzoros CS. Irisin in patients with nonalcoholic fatty liver disease. *Metabolism* 2014;63(2): 207-17.
63 Polyzos SA, Kountouras J, Shields K, Mantzoros CS. Irisin: A renaissance in metabolism? *Metabolism* 2013;62(8): 1037-44.
64 Polyzos SA, Mathew H, Mantzoros CS. Irisin: A true, circulating hormone. *Metabolism* 2015;64(12): 1611-8.
65 Cork SC, Richards JE, Holt MK, Gribble FM, Reimann F, Trapp S. Distribution and characterisation of glucagon-like peptide-1 receptor expressing cells in the mouse brain. *Mol Metab* 2015;4(10): 718-31.
66 Maniscalco JW, Zheng H, Gordon PJ, Rinaman L. Negative energy balance blocks neural and behavioral responses to acute stress by "silencing" central glucagon-like peptide 1 signaling in rats. 2015;35(30): 10701-14.
67 Tweedie D, Rachmany L, Rubovitch V, Li Y, Holloway HW, Lehrmann E, et al. Blast traumatic brain injury-induced cognitive deficits are attenuated by preinjury or postinjury treatment with the glucagon-like peptide-1 receptor agonist, exendin-4. *Alzheimers Dement* 2015.
68 van Bloemendaal L, Veltman DJ, Ten Kulve JS, Drent ML, Barkhof F, Diamant M, et al. Emotional eating is associated with increased brain responses to food-cues and reduced sensitivity to glp-1 receptor activation. *Obesity (Silver Spring)* 2015;23(10): 2075-82.
69 Wang XF, Liu JJ, Xia J, Liu J, Mirabella V, Pang ZP. Endogenous glucagon-like peptide-1 suppresses high-fat food intake by reducing synaptic drive onto mesolimbic dopamine neurons. *J Neurosci* 2015;12(5): 726-33.
70 Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjoth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The scale diabetes randomized clinical trial. *Jama* 2015;314(7): 687-99.
71 Nuffer WA, Trujillo JM. Liraglutide: A new option for the treatment of obesity. *Pharmacotherapy* 2015;35(10): 926-34.

72 Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015;373(1): 11-22.
73 Delgado JM, Anand BK. Increase of food intake induced by electrical stimulation of the lateral hypothalamus. *Am J Physiol* 1953;172(1): 162-8.
74 Mogenson GJ. Stability and modification of consummatory behaviors elicited by electrical stimulation of the hypothalamus. *Physiol Behav* 1971;6(3): 255-60.
75 Stephan FK, Valenstein ES, Zucker I. Copulation and eating during electrical stimulation of the rat hypothalamus. *Physiol Behav* 1971;7(4): 587-93.
76 Sani S, Jobe K, Smith A, Kordower JH, Bakay RA. Deep brain stimulation for treatment of obesity in rats. *J Neurosurg* 2007;107(4): 809-13.
77 Stenger J, Fournier T, Bielajew C. The effects of chronic ventromedial hypothalamic stimulation on weight gain in rats. *Physiol Behav* 1991;50(6): 1209-13.
78 Bielajew C, Stenger J, Schindler D. Factors that contribute to the reduced weight gain following chronic ventromedial hypothalamic stimulation. *Behav Brain Res* 1994;62(2): 143-8.
79 Lehmkuhle MJ, Mayes SM, Kipke DR. Unilateral neuromodulation of the ventromedial hypothalamus of the rat through deep brain stimulation. *J Neural Eng* 2010;7(3): 036006.
80 Lacan G, De Salles AA, Gorgulho AA, Krahl SE, Frighetto L, Behnke EJ, et al. Modulation of food intake following deep brain stimulation of the ventromedial hypothalamus in the vervet monkey. Laboratory investigation. *J Neurosurg* 2008;108(2): 336-42.
81 Geha PY, Aschenbrenner K, Felsted J, O'Malley SS, Small DM. Altered hypothalamic response to food in smokers. *Am J Clin Nutr* 2013;97(1): 15-22.
82 Baik JH. Dopamine signaling in food addiction: Role of dopamine d2 receptors. *BMB Rep* 2013;46(11): 519-26.
83 Blum K, Thanos PK, Gold MS. Dopamine and glucose, obesity, and reward deficiency syndrome. *Front Psychol* 2014;5: 919.
84 Burger KS, Stice E. Variability in reward responsivity and obesity: Evidence from brain imaging studies. *Curr Drug Abuse Rev* 2011;4(3): 182-9.
85 DiLeone RJ, Taylor JR, Picciotto MR. The drive to eat: Comparisons and distinctions between mechanisms of food reward and drug addiction. *Nat Neurosci* 2012;15(10): 1330-5.
86 Figlewicz DP. Adiposity signals and food reward: Expanding the cns roles of insulin and leptin. *Am J Physiol Regul Integr Comp Physiol* 2003;284(4): R882-92.
87 Gosnell BA, Levine AS. Reward systems and food intake: Role of opioids. *Int J Obes (Lond)* 2009;33 Suppl 2: S54-8.
88 Kelley M, Khan NA, Rolls ET. Taste, olfactory, and food reward value processing in the brain. *Adv Nutr* 2015;127-128: 64-90.
89 King BM. The modern obesity epidemic, ancestral hunter-gatherers, and the sensory/reward control of food intake. *Am Psychol* 2013;68(2): 88-96.
90 Michaelides M, Thanos PK, Volkow ND, Wang GJ. Translational neuroimaging in drug addiction and obesity. *Ilar j* 2012;53(1): 59-68.
91 Murray S, Tulloch A, Gold MS, Avena NM. Hormonal and neural mechanisms of food reward, eating behaviour and obesity. *Nat Rev Endocrinol* 2014;10(9): 540-52.
92 Smith DG, Robbins TW. The neurobiological underpinnings of obesity and binge eating: A rationale for adopting the food addiction model. *Biol Psychiatry* 2013;73(9): 804-10.
93 Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE. The contribution of brain reward circuits to the obesity epidemic. *Neurosci Biobehav Rev* 2013;37(9 Pt A): 2047-58.

94 Volkow ND, Wang GJ, Fowler JS, Tomasi D, Baler R. Food and drug reward: Overlapping circuits in human obesity and addiction. *Curr Top Behav Neurosci* 2012;11: 1-24.
95 Volkow ND, Wang GJ, Tomasi D, Baler RD. The addictive dimensionality of obesity. *Biol Psychiatry* 2013;73(9): 811-8.
96 Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: Neurobiological overlaps. *Obes Rev* 2013;14(1): 2-18.
97 Wang GJ, Volkow ND, Fowler JS. The role of dopamine in motivation for food in humans: Implications for obesity. *Expert Opin Ther Targets* 2002;6(5): 601-9.
98 Wang GJ, Volkow ND, Thanos PK, Fowler JS. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: A concept review. *J Addict Dis* 2004;23(3): 39-53.
99 Wise RA. Dual roles of dopamine in food and drug seeking: The drive-reward paradox. *Biol Psychiatry* 2013;73(9): 819-26.
100 Ziauddeen H, Alonso-Alonso M, Hill JO. Obesity and the neurocognitive basis of food reward and the control of intake. 2015;6(4): 474-86.
101 Dunn JP, Kessler RM, Feurer ID, Volkow ND, Patterson BW, Ansari MS, et al. Relationship of dopamine type 2 receptor binding potential with fasting neuroendocrine hormones and insulin sensitivity in human obesity. *Diabetes Care* 2012;35(5): 1105-11.
102 Thanos PK, Michaelides M, Piyis YK, Wang GJ, Volkow ND. Food restriction markedly increases dopamine d2 receptor (d2r) in a rat model of obesity as assessed with in-vivo mupet imaging ([11c] raclopride) and in-vitro ([3h] spiperone) autoradiography. *Synapse* 2008;62(1): 50-61.
103 Dunn JP, Cowan RL, Volkow ND, Feurer ID, Li R, Williams DB, et al. Decreased dopamine type 2 receptor availability after bariatric surgery: Preliminary findings. *Brain Res* 2010;1350: 123-30.
104 Volkow ND, Wang GJ, Telang F, Fowler JS, Thanos PK, Logan J, et al. Low dopamine striatal d2 receptors are associated with prefrontal metabolism in obese subjects: Possible contributing factors. *Neuroimage* 2008;42(4): 1537-43.
105 Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. *Lancet* 2001;357(9253): 354-7.
106 Michaelides M, Thanos PK, Kim R, Cho J, Ananth M, Wang GJ, et al. Pet imaging predicts future body weight and cocaine preference. *Neuroimage* 2012;59(2): 1508-13.
107 Volkow ND, Wang GJ, Maynard L, Jayne M, Fowler JS, Zhu W, et al. Brain dopamine is associated with eating behaviors in humans. *Int J Eat Disord* 2003;33(2): 136-42.
108 Johnson PM, Kenny PJ. Dopamine d2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci* 2010;13(5): 635-41.
109 Rothemund Y, Preuschhof C, Bohner G, Bauknecht HC, Klingebiel R, Flor H, et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage* 2007;37(2): 410-21.
110 Stice E, Yokum S, Bohon C, Marti N, Smolen A. Reward circuitry responsivity to food predicts future increases in body mass: Moderating effects of drd2 and drd4. *Neuroimage* 2010;50(4): 1618-25.
111 Beaver JD, Lawrence AD, van Ditzhuijzen J, Davis MH, Woods A, Calder AJ. Individual differences in reward drive predict neural responses to images of food. *J Neurosci* 2006;26(19): 5160-6.

112 Pelchat ML, Johnson A, Chan R, Valdez J, Ragland JD. Images of desire: Food-craving activation during fmri. *Neuroimage* 2004;23(4): 1486-93.
113 Yokum S, Ng J, Stice E. Attentional bias to food images associated with elevated weight and future weight gain: An fmri study. *Obesity (Silver Spring)* 2011;19(9): 1775-83.
114 Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: A functional magnetic resonance imaging study. *J Abnorm Psychol* 2008;117(4): 924-35.
115 Colantuoni C, Rada P, McCarthy J, Patten C, Avena NM, Chadeayne A, et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res* 2002;10(6): 478-88.
116 Dong C, Sanchez LE, Price RA. Relationship of obesity to depression: A family-based study. *Int J Obes Relat Metab Disord* 2004;28(6): 790-5.
117 Novick JS, Stewart JW, Wisniewski SR, Cook IA, Manev R, Nierenberg AA, et al. Clinical and demographic features of atypical depression in outpatients with major depressive disorder: Preliminary findings from star*d. *J Clin Psychiatry* 2005;66(8): 1002-11.
118 Potenza MN. Obesity, food, and addiction: Emerging neuroscience and clinical and public health implications. *Neuropsychopharmacology* 2014;39(1): 249-50.
119 Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: Evidence from the alameda county study. *Int J Obes Relat Metab Disord* 2003;27(4): 514-21.
120 Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, et al. Association between obesity and psychiatric disorders in the us adult population. *Arch Gen Psychiatry* 2006;63(7): 824-30.
121 Macht M. Characteristics of eating in anger, fear, sadness and joy. *Appetite* 1999;33(1): 129-39.
122 Canetti L, Bachar E, Berry EM. Food and emotion. *Behav Processes* 2002;60(2): 157-64.
123 Farr OM, Sloan DM, Keane TM, Mantzoros CS. Stress- and ptsd-associated obesity and metabolic dysfunction: A growing problem requiring further research and novel treatments. *Metabolism* 2014;63(12): 1463-8.
124 O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ. Neural responses during anticipation of a primary taste reward. *Neuron* 2002;33(5): 815-26.
125 Small DM, Veldhuizen MG, Felsted J, Mak YE, McGlone F. Separable substrates for anticipatory and consummatory food chemosensation. *Neuron* 2008;57(5): 786-97.
126 Stoeckel LE, Weller RE, Cook EW, 3rd, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* 2008;41(2): 636-47.
127 Holsen LM, Zarcone JR, Brooks WM, Butler MG, Thompson TI, Ahluwalia JS, et al. Neural mechanisms underlying hyperphagia in prader-willi syndrome. *Obesity (Silver Spring)* 2006;14(6): 1028-37.
128 Boutelle KN, Wierenga CE, Bischoff-Grethe A, Melrose AJ, Grenesko-Stevens E, Paulus MP, et al. Increased brain response to appetitive tastes in the insula and amygdala in obese compared with healthy weight children when sated. *Int J Obes (Lond)* 2015;39(4): 620-8.
129 Jastreboff AM, Lacadie C, Seo D, Kubat J, Van Name MA, Giannini C, et al. Leptin is associated with exaggerated brain reward and emotion responses to food images in adolescent obesity. *Diabetes Care* 2014;37(11): 3061-8.

130 Mehta S, Melhorn SJ, Smeraglio A, Tyagi V, Grabowski T, Schwartz MW, et al. Regional brain response to visual food cues is a marker of satiety that predicts food choice. *Am J Clin Nutr* 2012;96(5): 989-99.
131 Sun X, Kroemer NB, Veldhuizen MG, Babbs AE, de Araujo IE, Gitelman DR, et al. Basolateral amygdala response to food cues in the absence of hunger is associated with weight gain susceptibility. *J Neurosci* 2015;35(20): 7964-76.
132 Ulrich-Lai YM, Christiansen AM, Wang X, Song S, Herman JP. Statistical modeling implicates neuroanatomical circuit mediating stress relief by 'comfort' food. *Brain Struct Funct* 2015.
133 Martin AA, Davidson TL. Human cognitive function and the obesogenic environment. *Physiol Behav* 2014;136: 185-93.
134 Parent MB, Darling JN, Henderson YO. Remembering to eat: Hippocampal regulation of meal onset. *Am J Physiol Regul Integr Comp Physiol* 2014;306(10): R701-13.
135 Robinson E, Aveyard P, Daley A, Jolly K, Lewis A, Lycett D, et al. Eating attentively: A systematic review and meta-analysis of the effect of food intake memory and awareness on eating. *Am J Clin Nutr* 2013;97(4): 728-42.
136 Cornell CE, Rodin J, Weingarten H. Stimulus-induced eating when satiated. *Physiol Behav* 1989;45(4): 695-704.
137 Petrovich GD, Ross CA, Holland PC, Gallagher M. Medial prefrontal cortex is necessary for an appetitive contextual conditioned stimulus to promote eating in sated rats. *J Neurosci* 2007;27(24): 6436-41.
138 Reppucci CJ, Petrovich GD. Learned food-cue stimulates persistent feeding in sated rats. *Appetite* 2012;59(2): 437-47.
139 Weingarten HP. Meal initiation controlled by learned cues: Basic behavioral properties. *Appetite* 1984;5(2): 147-58.
140 Rolls ET. Functions of the orbitofrontal and pregenual cingulate cortex in taste, olfaction, appetite and emotion. *Acta Physiol Hung* 2008;95(2): 131-64.
141 Smith GP. The controls of eating: A shift from nutritional homeostasis to behavioral neuroscience. *Nutrition* 2000;16(10): 814-20.
142 Wang GJ, Tomasi D, Backus W, Wang R, Telang F, Geliebter A, et al. Gastric distention activates satiety circuitry in the human brain. *Neuroimage* 2008;39(4): 1824-31.
143 Wang GJ, Yang J, Volkow ND, Telang F, Ma Y, Zhu W, et al. Gastric stimulation in obese subjects activates the hippocampus and other regions involved in brain reward circuitry. *Proc Natl Acad Sci U S A* 2006;103(42): 15641-5.
144 Carlini VP, Varas MM, Cragnolini AB, Schioth HB, Scimonelli TN, de Barioglio SR. Differential role of the hippocampus, amygdala, and dorsal raphe nucleus in regulating feeding, memory, and anxiety-like behavioral responses to ghrelin. *Biochem Biophys Res Commun* 2004;313(3): 635-41.
145 Chen L, Xing T, Wang M, Miao Y, Tang M, Chen J, et al. Local infusion of ghrelin enhanced hippocampal synaptic plasticity and spatial memory through activation of phosphoinositide 3-kinase in the dentate gyrus of adult rats. *Eur J Neurosci* 2011;33(2): 266-75.
146 Farr SA, Banks WA, Morley JE. Effects of leptin on memory processing. *Peptides* 2006;27(6): 1420-5.
147 Oomura Y, Hori N, Shiraishi T, Fukunaga K, Takeda H, Tsuji M, et al. Leptin facilitates learning and memory performance and enhances hippocampal ca1 long-term potentiation and camk ii phosphorylation in rats. *Peptides* 2006;27(11): 2738-49.

148 Davidson TL, Chan K, Jarrard LE, Kanoski SE, Clegg DJ, Benoit SC. Contributions of the hippocampus and medial prefrontal cortex to energy and body weight regulation. *Hippocampus* 2009;19(3): 235-52.
149 Francis HM, Stevenson RJ. Higher reported saturated fat and refined sugar intake is associated with reduced hippocampal-dependent memory and sensitivity to interoceptive signals. *Behav Neurosci* 2011;125(6): 943-55.
150 Hebben N, Corkin S, Eichenbaum H, Shedlack K. Diminished ability to interpret and report internal states after bilateral medial temporal resection: Case h.M. *Behav Neurosci* 1985;99(6): 1031-9.
151 Higgs S, Williamson AC, Rotshtein P, Humphreys GW. Sensory-specific satiety is intact in amnesics who eat multiple meals. *Psychol Sci* 2008;19(7): 623-8.
152 Beilharz JE, Maniam J, Morris MJ. Short exposure to a diet rich in both fat and sugar or sugar alone impairs place, but not object recognition memory in rats. *Brain Behav Immun* 2014;37: 134-41.
153 Darling JN, Ross AP, Bartness TJ, Parent MB. Predicting the effects of a high-energy diet on fatty liver and hippocampal-dependent memory in male rats. *Obesity (Silver Spring)* 2013;21(5): 910-7.
154 Davidson TL, Hargrave SL, Swithers SE, Sample CH, Fu X, Kinzig KP, et al. Inter-relationships among diet, obesity and hippocampal-dependent cognitive function. *Neuroscience* 2013;253: 110-22.
155 Farr SA, Yamada KA, Butterfield DA, Abdul HM, Xu L, Miller NE, et al. Obesity and hypertriglyceridemia produce cognitive impairment. *Endocrinology* 2008;149(5): 2628-36.
156 Banks WA, Farr SA, Morley JE. The effects of high fat diets on the blood-brain barrier transport of leptin: Failure or adaptation? *Physiol Behav* 2006;88(3): 244-8.
157 Pallebage-Gamarallage M, Lam V, Takechi R, Galloway S, Clark K, Mamo J. Restoration of dietary-fat induced blood-brain barrier dysfunction by anti-inflammatory lipid-modulating agents. *Lipids Health Dis* 2012;11: 117.
158 Puig KL, Floden AM, Adhikari R, Golovko MY, Combs CK. Amyloid precursor protein and proinflammatory changes are regulated in brain and adipose tissue in a murine model of high fat diet-induced obesity. *PLoS One* 2012;7(1): e30378.
159 Ross AP, Bruggeman EC, Kasumu AW, Mielke JG, Parent MB. Non-alcoholic fatty liver disease impairs hippocampal-dependent memory in male rats. *Physiol Behav* 2012;106(2): 133-41.
160 Joussen AM, Poulaki V, Le ML, Koizumi K, Esser C, Janicki H, et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. *Faseb j* 2004;18(12): 1450-2.
161 Tsuda M, Inoue K, Salter MW. Neuropathic pain and spinal microglia: A big problem from molecules in "small" glia. *Trends Neurosci* 2005;28(2): 101-7.
162 Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: Direct role in obesity-linked insulin resistance. *Science* 1993;259(5091): 87-91.
163 Wolburg H, Lippoldt A. Tight junctions of the blood-brain barrier: Development, composition and regulation. *Vascul Pharmacol* 2002;38(6): 323-37.
164 Milanski M, Degasperi G, Coope A, Morari J, Denis R, Cintra DE, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of tlr4 signaling in hypothalamus: Implications for the pathogenesis of obesity. *J Neurosci* 2009;29(2): 359-70.
165 Thaler JP, Choi SJ, Schwartz MW, Wisse BE. Hypothalamic inflammation and energy homeostasis: Resolving the paradox. *Front Neuroendocrinol* 2010;31(1): 79-84.

166 Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* 2011;333(6048): 1456-8.
167 Andre C, Dinel AL, Ferreira G, Laye S, Castanon N. Diet-induced obesity progressively alters cognition, anxiety-like behavior and lipopolysaccharide-induced depressive-like behavior: Focus on brain indoleamine 2,3-dioxygenase activation. *Brain Behav Immun* 2014;41: 10-21.
168 Doolan KJ, Breslin G, Hanna D, Gallagher AM. Attentional bias to food-related visual cues: Is there a role in obesity? *Proc Nutr Soc* 2015;74(1): 37-45.
169 Leland DS, Pineda JA. Effects of food-related stimuli on visual spatial attention in fasting and nonfasting normal subjects: Behavior and electrophysiology. *Clin Neurophysiol* 2006;117(1): 67-84.
170 Placanica JL, Faunce GJ, Soames Job RF. The effect of fasting on attentional biases for food and body shape/weight words in high and low eating disorder inventory scorers. *Int J Eat Disord* 2002;32(1): 79-90.
171 Ahern AL, Field M, Yokum S, Bohon C, Stice E. Relation of dietary restraint scores to cognitive biases and reward sensitivity. *Appetite* 2010;55(1): 61-8.
172 Brignell C, Griffiths T, Bradley BP, Mogg K. Attentional and approach biases for pictorial food cues. Influence of external eating. *Appetite* 2009;52(2): 299-306.
173 Van Strien T, Schippers GM, Cox WM. On the relationship between emotional and external eating behavior. *Addict Behav* 1995;20(5): 585-94.
174 Castellanos EH, Charboneau E, Dietrich MS, Park S, Bradley BP, Mogg K, et al. Obese adults have visual attention bias for food cue images: Evidence for altered reward system function. *Int J Obes (Lond)* 2009;33(9): 1063-73.
175 Corbetta M, Kincade JM, Shulman GL. Neural systems for visual orienting and their relationships to spatial working memory. *J Cogn Neurosci* 2002;14(3): 508-23.
176 Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 2002;3(3): 201-15.
177 Fuhrer D, Zysset S, Stumvoll M. Brain activity in hunger and satiety: An exploratory visually stimulated fmri study. *Obesity (Silver Spring)* 2008;16(5): 945-50.
178 Schur EA, Kleinhans NM, Goldberg J, Buchwald D, Schwartz MW, Maravilla K. Activation in brain energy regulation and reward centers by food cues varies with choice of visual stimulus. *Int J Obes (Lond)* 2009;33(6): 653-61.
179 Tuulari JJ, Karlsson HK, Hirvonen J, Salminen P, Nuutila P, Nummenmaa L. Neural circuits for cognitive appetite control in healthy and obese individuals: An fmri study. *PLoS One* 2015;10(2): e0116640.
180 Schonberg T, Bakkour A, Hover AM, Mumford JA, Poldrack RA. Influencing food choices by training: Evidence for modulation of frontoparietal control signals. *J Cogn Neurosci* 2014;26(2): 247-68.
181 Gearhardt AN, Yokum S, Stice E, Harris JL, Brownell KD. Relation of obesity to neural activation in response to food commercials. *Soc Cogn Affect Neurosci* 2014;9(7): 932-8.
182 Cornier MA, McFadden KL, Thomas EA, Bechtell JL, Eichman LS, Bessesen DH, et al. Differences in the neuronal response to food in obesity-resistant as compared to obesity-prone individuals. *Physiol Behav* 2013;110-111: 122-8.
183 Murdaugh DL, Cox JE, Cook EW, 3rd, Weller RE. Fmri reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *Neuroimage* 2012;59(3): 2709-21.

184 Aron AR. From reactive to proactive and selective control: Developing a richer model for stopping inappropriate responses. *Biol Psychiatry* 2011;69(12): e55-68.
185 Anzman-Frasca S, Francis LA, Birch LL. Inhibitory control is associated with psychosocial, cognitive, and weight outcomes in a longitudinal sample of girls. *Trans Issues Psychol Sci* 2015;1(3): 203-16.
186 Blanco-Gomez A, Ferre N, Luque V, Cardona M, Gispert-Llaurado M, Escribano J, et al. Being overweight or obese is associated with inhibition control in children from six to ten years of age. *Acta Paediatr* 2015;104(6): 619-25.
187 Chamberlain SR, Derbyshire KL, Leppink E, Grant JE. Obesity and dissociable forms of impulsivity in young adults. *CNS Spectr* 2015;20(5): 500-7.
188 He Q, Xiao L, Xue G, Wong S, Ames SL, Schembre SM, et al. Poor ability to resist tempting calorie rich food is linked to altered balance between neural systems involved in urge and self-control. *Nutr J* 2014;13: 92.
189 Khan NA, Raine LB, Drollette ES, Scudder MR, Cohen NJ, Kramer AF, et al. The relationship between total water intake and cognitive control among prepubertal children. *Ann Nutr Metab* 2015;66 Suppl 3: 38-41.
190 Kullmann S, Heni M, Veit R, Scheffler K, Machann J, Haring HU, et al. Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. *Diabetes Care* 2015;38(6): 1044-50.
191 Reyes S, Peirano P, Peigneux P, Lozoff B, Algarin C. Inhibitory control in otherwise healthy overweight 10-year-old children. *Int J Obes (Lond)* 2015;39(8): 1230-5.
192 Svaldi J, Naumann E, Trentowska M, Schmitz F. General and food-specific inhibitory deficits in binge eating disorder. *Int J Eat Disord* 2014;47(5): 534-42.
193 Wirt T, Hundsdorfer V, Schreiber A, Kesztyus D, Steinacker JM. Associations between inhibitory control and body weight in german primary school children. *Eat Behav* 2014;15(1): 9-12.
194 Wirt T, Schreiber A, Kesztyus D, Steinacker JM. Early life cognitive abilities and body weight: Cross-sectional study of the association of inhibitory control, cognitive flexibility, and sustained attention with bmi percentiles in primary school children. *J Obes* 2015;2015: 534651.
195 Nederkoorn C, Jansen E, Mulkens S, Jansen A. Impulsivity predicts treatment outcome in obese children. *Behav Res Ther* 2007;45(5): 1071-5.
196 Camus M, Halelamien N, Plassmann H, Shimojo S, O'Doherty J, Camerer C, et al. Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex decreases valuations during food choices. *Eur J Neurosci* 2009;30(10): 1980-8.
197 Hare TA, Camerer CF, Rangel A. Self-control in decision-making involves modulation of the vmpfc valuation system. *Science* 2009;324(5927): 646-8.
198 Chapman CD, Benedict C, Brooks SJ, Schioth HB. Lifestyle determinants of the drive to eat: A meta-analysis. *Am J Clin Nutr* 2012;96(3): 492-7.
199 Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: Evidence of systems pathology. *Philos Trans R Soc Lond B Biol Sci* 2008;363(1507): 3191-200.
200 Volkow ND, Wang GJ, Telang F, Fowler JS, Goldstein RZ, Alia-Klein N, et al. Inverse association between bmi and prefrontal metabolic activity in healthy adults. *Obesity (Silver Spring)* 2009;17(1): 60-5.
201 Willette AA, Kapogiannis D. Does the brain shrink as the waist expands? *Ageing Res Rev* 2015;20: 86-97.

202 Alosco ML, Galioto R, Spitznagel MB, Strain G, Devlin M, Cohen R, et al. Cognitive function after bariatric surgery: Evidence for improvement 3 years after surgery. *Am J Surg* 2014;207(6): 870-6.

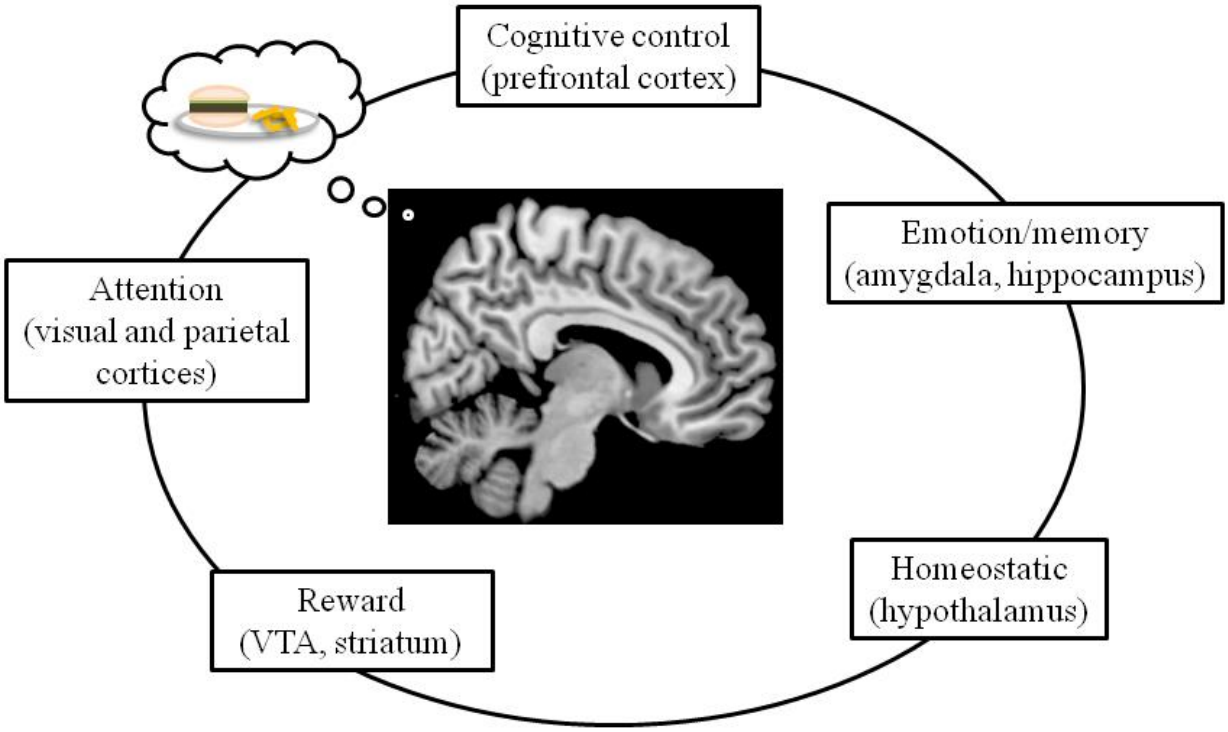

Figure 1

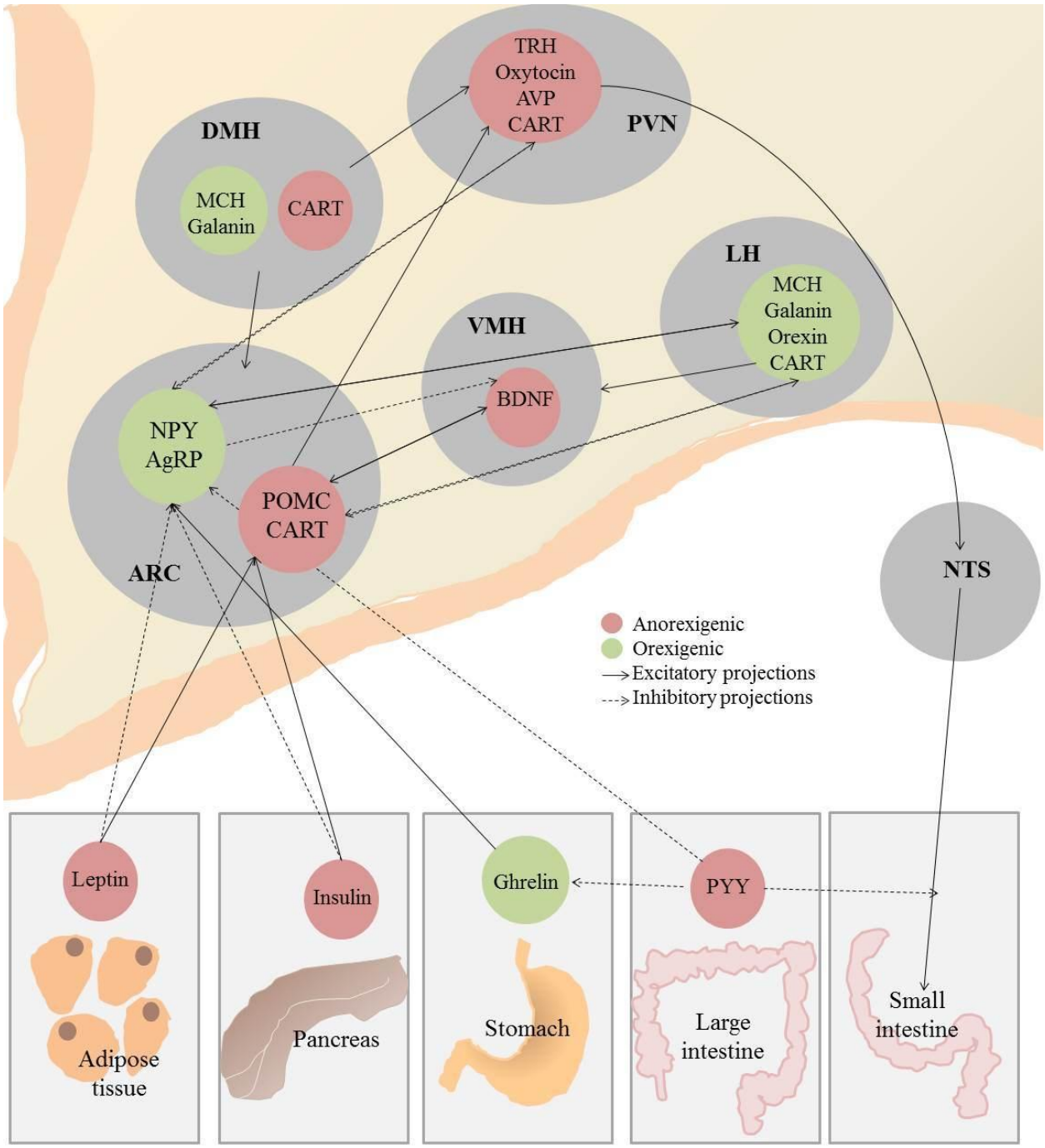

Figure 2

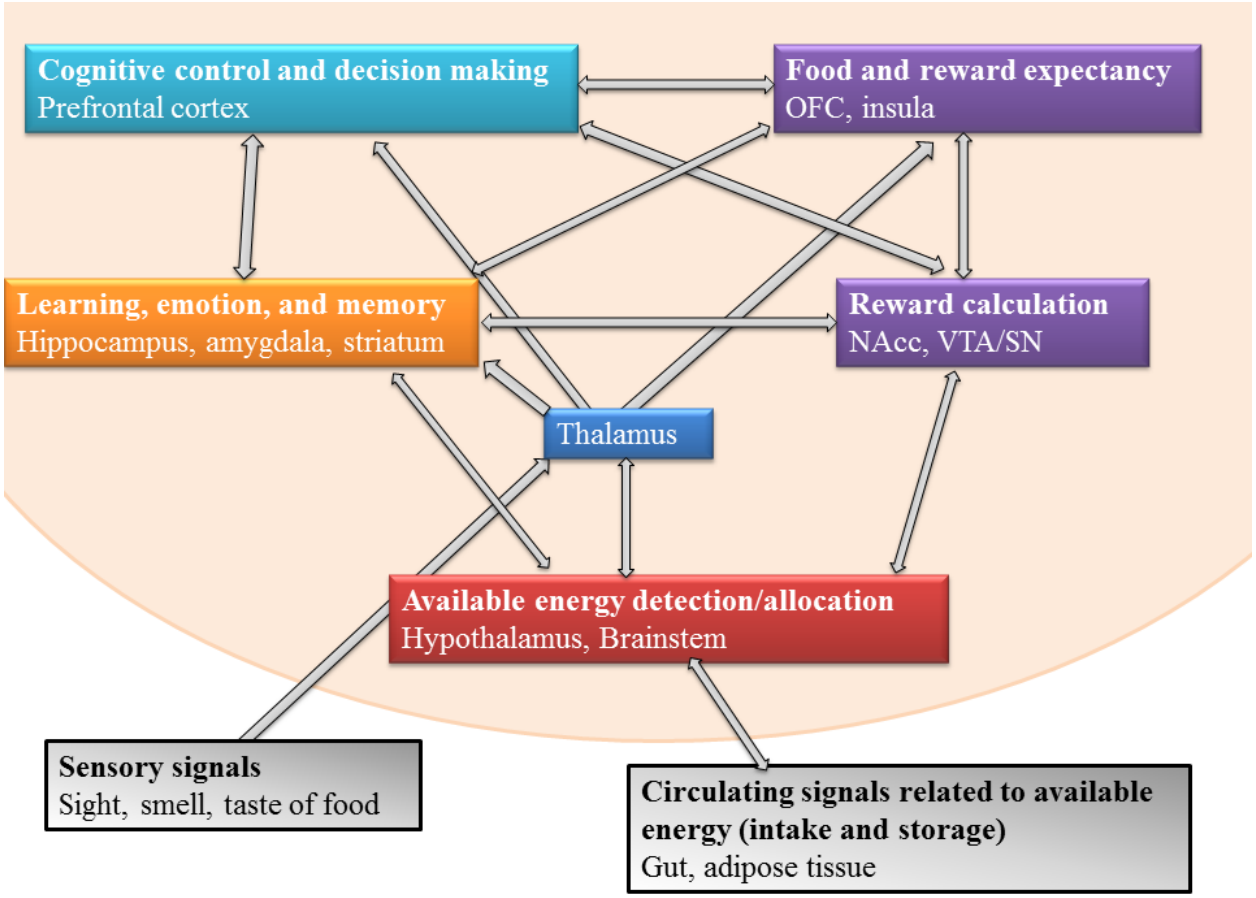

Figure 3

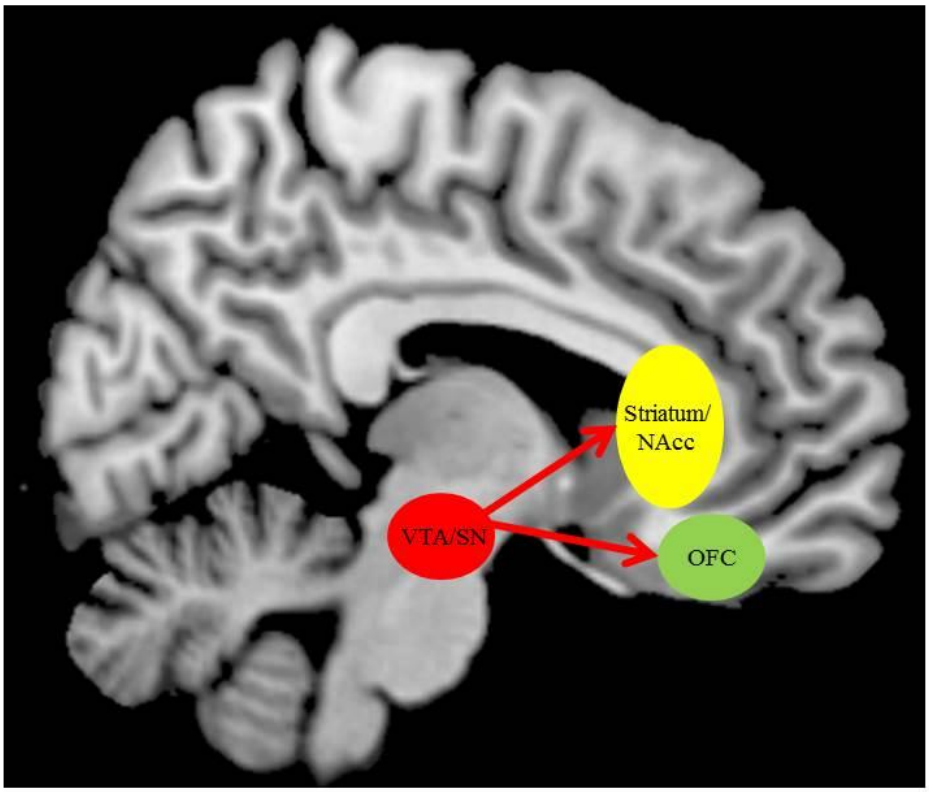

Figure 4

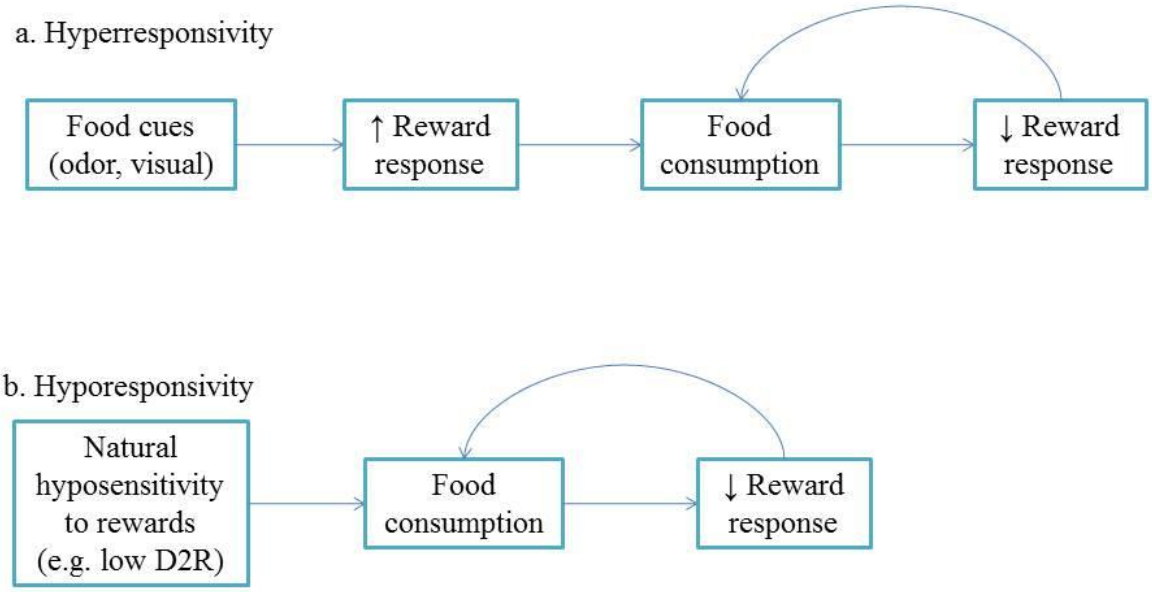

Figure 5

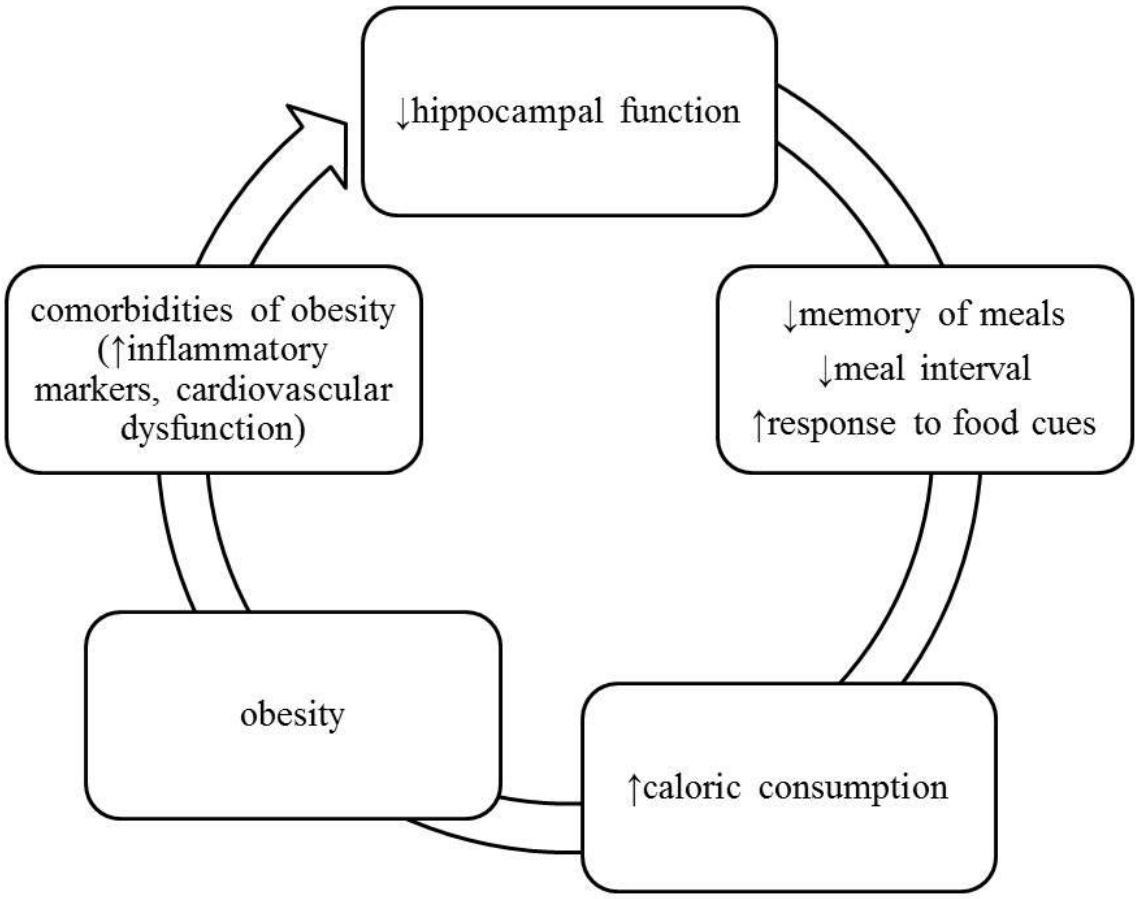

Figure 6

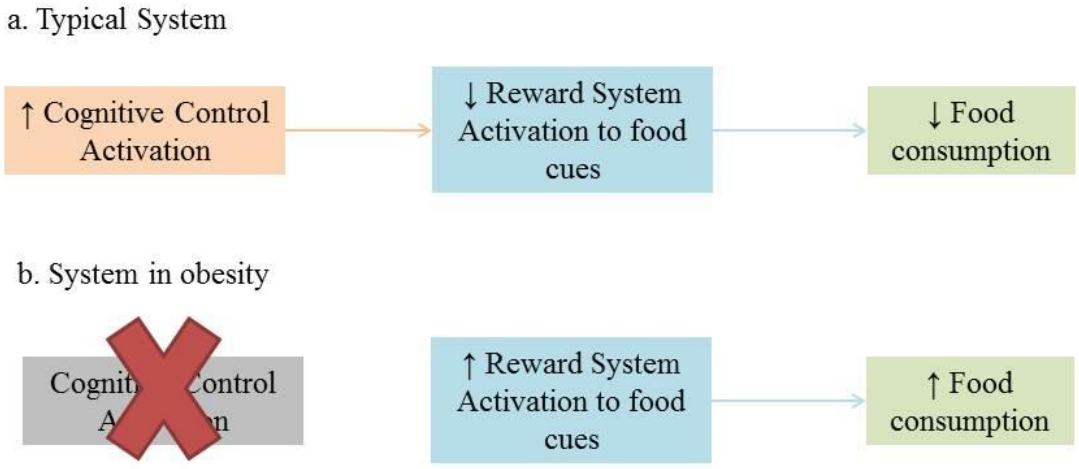

Figure 7