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

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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, but 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.

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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 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 nonexclusive 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.

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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

Figure 1.

Control of eating in human brain is regulated by several systems including the 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**).