Food Addiction and Neuroimaging

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Abstract: Obesity has become a serious epidemic and one of the leading global health problems. However, much of the current debate has been fractious, and etiologies of obesity have been attributed to eating behavior (i.e. fast food consumption), personality, depression, addiction or genetics. One of the interesting new hypotheses for explaining the development of obesity involves a food addiction model, which suggests that food is not eaten as much for survival as pleasure and that hedonic overeating is relevant to both substance-related disorders and eating disorders. Accumulating evidence has shown that there are a number of shared neural and hormonal pathways as well as distinct differences in these pathways that may help researchers discover why certain individuals continue to overeat despite health and other consequences, and becomes more and more obese. Functional neuroimaging studies have further revealed that pleasant smelling, looking, and tasting food has reinforcing characteristics similar to drugs of abuse. Many of the brain changes reported for hedonic eating and obesity are also seen in various types of addictions. Most importantly, overeating and obesity may have an acquired drive similar to drug addiction with respect to motivation and incentive craving. In both cases, the desire and continued satisfaction occur after early and repeated exposure to stimuli. The acquired drive for eating food and relative weakness of the satiety signal would cause an imbalance between the drive and hunger/reward centers in the brain and their regulation. In the current paper, we first provide a summary of literature on food addition from eight different perspectives, and then we proposed a research paradigm that may allow screening of new pharmacological treatment on the basis of functional magnetic resonance imaging (fMRI).

Keywords: Obesity, overeating, dopamine, food addiction, pharmacological treatment development, reinforcement, neuroimaging.

INTRODUCTION

The United States is facing a pervasive and devastating obesity epidemic. In the United States, approximately 90 million Americans are obese; more than 400,000 deaths related to obesity or associated diseases occur annually in the States [1]. While much attention has been given to obesity in the Western world, developing countries are not immune to the globesity epidemic either [2]. Lately, the prevalence of obesity is leveling off in woman but is increasing in men, children and adolescents [1]. Obesity is associated with an increased risk of morbidity and mortality, which places a sense of urgency to understand the processes that have contributed to this epidemic. More recently, the notion that obesity might be a form of addiction originating from a variety of psychological and physiological causes has been gaining popularity [3]. Advocates of this theory claim that the study of drug addiction may also inform our understanding of obesity and help predict newer and more effective treatment approaches [4]. As an addictive process, it can be defined as a chronic relapsing problem caused by various fundamental factors that increase craving for food or food-related substances leading to a state of heightened pleasure, energy or excitement. Food addiction most often results in the loss of control, impulsive and compulsive behavior that arises from emotional and environmental conditions and a dependence on the feelings that food produces in the brain. Americans eat out often and are exposed to increasingly large food portions are served in restaurants and fast food outlets. Advertisements on the television and internet elicit cravings by food cues thereby encouraging children and adults to snack or seek food despite lack of hunger signals. In the present paper we first provide a summary of literature on food addition from the perspectives of definition, human and animal models, neuroendocrinological, hypothalamic signaling and reward systems, food cues, and neuroimaging studies. Finally, we proposed a paradigm that conducts fMRI scanning of young healthy subjects of normal weight to measure different brain activation by visual images of highly rewarding foods (high caloric food like hamburger, chips) compared with images of non-food in resting states. It may allow screening of new pharmacological treatment on the basis of fMRI.

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FOOD ADDICTION

Traditional addiction research focuses on drugs of abuse, such as cocaine, nicotine, morphine and alcohol. It implies psychological dependence, and thus is a mental or cognitive problem that is often referred to as 'substance dependence,' which is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [5]. However, a variety of addictions to non-drug entities, including gambling, sex and food have been investigated recently [6-14]. In general, food addiction is associated with substance related disorders [15] as well as eating disorders, although there is no clear definition for such condition. It has been noted in DSM V's proposed revision (http: //www.dsm5.org) that a recommendation for binge eating disorder [16] to be recognized as a free-standing diagnosis. It is also being recommended that the category of Eating Disorders be renamed as Eating and Feeding Disorders to reflect the proposed inclusion of feeding disorders. From a scientific standpoint, food addition can be defined as a chronic relapsing problem caused by various fundamental factors that increase craving for food or food related substance leading to a state of heightened pleasure, energy, or excitement [17-21]. There are also clinical accounts in which self-identified food addicts used food to self-regulate in order to escape a negative mood state [22]. One of the most commonly studied food cravings is carbohydrate craving, and the authors found that the combination of increased liking for carbohydrates in the context of decreased mood effects paralleled other addiction processes [23, 24]. Most food addiction results in the loss of control, impulsive and/or compulsive behavior arising from emotional and environment conditions and a psychological dependence on food [25, 26]. Eating behaviors are similar to those of other addiction behaviors since both affect the levels of dopamine (DA) in the

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mesolimbic dopaminergic system [20, 27]. For example, DA D2 receptors have a high prevalence of Tag1A1 allele [28, 29] and this allele has been linked to low levels of these receptors in obese individuals [29, 30]. Thus, these individuals use food to raise their DA levels through positive reinforcement [31]. The findings disclosed that the mesolimbic dopamine system plays a critical role in preference for high energy diets and results in abnormal eating behavior (i.e. hyperphagia), eating disorders and dietary obesity [32-34].

EVIDENCE FROM PRADER-WILLI SYNDROME

Prader-Willi Syndrome (PWS) is a genetic imprinting disorder that results in profound hyperphagia and early childhood obesity. One characteristic of the disease is a marked obsessive compulsive drive to overeat not only food but also inanimate objects, which can result from excessive, pathologic, reinforcement produced by the ingested items themselves [35]. PWS is associated with substance dependence and was chosen as a well defined genetic model since it may help explain certain neurophysiologic mechanisms that affect appetite and food addiction [36]. Thus, it can be more thoroughly investigated and applied to human obesity conditions than animal models.

PWS patients are identified as being genetically obese since childhood. About 70% of cases are caused by a paternal genetic deletion on chromosome 15 (15q11-13), whereas 25% are from a maternal uniparental disomy of chromosome 15 [37]. The remaining 1-5% of PWS cases results from certain imprinting defects, which have a 50% risk potential to recur in future offspring [35, 38, 39]. There is a loss of specific brain genes such as MAGEL2, MKRN3, NDN, SNURF-SNRPN and sno-RNA that are misrouted or lost resulting in abnormal cortical development in patients diagnosed with PWS [40]. These genetic anomalies can be detected by DNA methylation analysis and in situ hybridization of the alleles [35].

Individuals with PWS are characterized as having dolichocephaly, almond-shaped eyes, small mouth, hands, and feet, decreased muscle tone [41], infantile hypotonia, hypogonadia, short stature, and early onset of obesity due to central dysfunction (around 18 to 36 months of age) [42]. They also show major disturbances in appetite, sleep, breathing, and metabolism regulation. Abnormal eating behavior is manifested by delayed satiety, premature return of hunger after eating a meal, seeking and hoarding food and food-related objects, and ingesting inanimate items [43] as well as excessive daytime drowsiness, poor ventilation, hypercapnia, and dental cavities [44]. Overall, many systems are affected by PWS such as the central nervous system (CNS), gastrointestinal, urogenital, cardiovascular, respiratory, and integumentary resulting in numerous medical conditions and disorders [35].

Miller *et al.* [43] hypothesized that the irregular reward processing of food stimuli in brain pathways caused the aberrant appetite, and these pathways involve the hypothalamus, frontal cortex, insula, and limbic/paralimbic areas. Furthermore, postmortem analyses have shown a decreased number of cells in the paraventricular nucleus (PVN) [45]. This is a crucial evidence for explaining why satiety is difficult to attain, since PVN is the hunger center of the brain that controls appetite [46]. Using the conditioned Granger causality method, Zhou *et al.* [47] found that there is strong influence of the amygdala (AMY) on the anterior cingulated cortex (ACC), which is more highly activated during an emotional task associated with feeding [43] compared to the brain activation of normal subjects during the resting state.

EVIDENCE OF FOOD ADDICTION FROM ANIMAL STUDIES

Animal studies have shown that the predisposition to food addiction in offspring can be caused by feeding rat mothers junk food consisting of fatty, sugary, and salty snacks during pregnancy and lactation [48]. Rodent offspring showed increased weight gain and body mass index (BMI) compared to controls, whereas their mothers displayed bingeing and overeating of junk food [48]. Thus, these findings may be applied to the diets of pregnant women in order for them to have healthy children with normal appetites and weight. Avena has developed a rat model of sucrose bingeing, rats are maintained on a diet of 12-h access to a 10% sucrose solution (or 25% glucose in earlier studies) and standard rodent chow and then followed by 12-h of sucrose and chow deprivation for a period of about one month. The findings of this model relate to a variety of factors associated with addictive behavior and with sugar classified as an addictive substance [9, 13, 49] because it follows the typical stages of the human addiction pathway of bingeing, withdrawal, craving, bingeing in a never-ending cycle.

Bingeing is defined as an "escalation of intake with a high proportion of intake at one time, usually after a period of voluntary abstinence or forced deprivation"[9]. Avena showed that after a month of binge eating (sugar or glucose), rats displayed a series of behaviors similar to the effects of drug abuse, including the escalation of everyday intake and increase in sugar intake during the first hour of daily access. Sucrose bingeing rats regulate their caloric intake by decreasing their chow consumption, which compensates for the extra calories obtained from sugar and thus resulting in a normal body weight [50]. Withdrawal is known to be caused by alteration in the opioid system [51], where DA decreases and acetylcholine (ACh) is released from the nucleus accumbens (N_{AC}). Signs of opiate-like withdrawal also emerge when the abused substance is removed; signs include production of DA, ACh and opioids similar in response to naloxone [51], often characterized by anxiety [52] and depressive behavior [9]. The third stage of dependence is craving, which happens after a prolonged period of abstinence and is defined by "increased efforts to obtain a substance of abuse or its associated cues as a result of dependence and abstinence" [9]. Craving is measured during sugar abstinence as enhanced responding for sugar [53]. During the study performed by Avena, rats with the binge access lever pressed for 23% more sugar than they ever did before and after two weeks of forced abstinence from sugar [53], which indicated the change in the motivational impact of sugar, leading enhanced intake. Except for the above diagnostic criteria, cross-sensitization is predominantly defined as "an increased locomotor response to a different drug or substance"[9]; or more simply stated, animals sensitized to one drug may show increased intake of a different drug. For example, rats previously bingeing on sugar will drink more than 9% alcohol compared to control groups with access to *ad libitum* sugar, *ad libitum* chow, or binge (12 h) chow only [53]. In terms of similarities to other forms of addiction, this data suggests that one drug acts as a gateway to another [9]. All of these definitions play a critical role in helping define and classify food (especially sugar) as a true addictive substance in comparison to the criteria for drug dependence as shown at least in rats [54]. In addition, other studies of rats suggest that the rats developed a dopamine-mediated addiction to palatable food [34, 55-57].

NEUROENDOCRINOLOGICAL EVIDENCE

Defining the endocrinology behind obesity is crucial to understanding food addiction and overeating behavior. A great deal of evidence suggests a similarity in the neurochemical response to drugs and to food. Both palatable food and drugs appear to activate the same mesolimbic dopamine reward system in the brains of humans and animals [14, 36, 58-60]. DA is a neurotransmitter known to play a critical role in motivation that is involved with reward processing and positive behavior reinforcement [20, 61, 62]. The mesolimbic DA projections from the ventral tegmental area (VTA) to the N_{AC} are well known for reinforcement behavior such as feeding [63]. The N_{AC} is important for several components of reward processing including increased food seeking behavior, in the learning of incentives, in the sense of motivation, in the feeling of satiety, and in stimulus salience processing [64]. Volkow [65] found

that when DA deficient mice were treated with DA in the dorsal striatum, feeding behavior was restored and the mice chose to eat more palatable food. Rats that were treated with DA in the N_{AC} also chose to eat more palatable food, even though they had no motivation to eat enough food to maintain normal function and stay alive. In another study, DA agonists were used to increase the portion size of meals and length of feeding, while long-term administration of DA increased body mass and feeding behavior [66]. In a conditioned response study, food deprived subjects that were pretreated with methylphenidate (MP) (20 mg orally) were scanned while stimulated with a neutral or food-related cues, and results demonstrated that food stimulation significantly increased DA in the dorsal striatum which correlated with the increases in self-reports of hunger and desire for food [65]. In addition, morbidly obese subjects have shown a higher level of baseline metabolism than normal in the somatosensory cortex [67], and this evidence demonstrated that the somatosensory cortex regulated DA activity in the human brain [68-70]. DA D2 receptors, which have been associated with feeding and addictive behaviors, play a role in reward seeking, prediction, expectation and motivation related behavior [71]. DA D2 receptor antagonists block food seeking behaviors that depend on reinforcement between the cues and the rewards that they predict as well as on palatable foods they like [72]. Stice [29] conducted a study that compared obese to lean individuals in response to receipt of a chocolate milkshake versus a tasteless solution. The results indicated that obese relative to lean humans have fewer DA D2 receptors in the striatum and that obese relative to lean rats have lower basal dopamine levels and reduced DA D2 receptor density. One study on healthy normal weight subjects showed that the tendency of the individuals with negative emotions to eat was negatively correlated with DA D2 receptor availability [73]. Wang [74] and Haltia [75] discovered that the lower DA D2 receptors had higher BMI in morbidly obese (BMI>40) and obese subjects respectively. Their findings are consistent with the results that blocking DA D2 receptors increases food intake and raises the risk for obesity [76].

In addition, many peripheral metabolic signals, such as insulin, leptin and ghrelin, directly or indirectly interact with midbrain DA pathways [77-79]. Most childhood obesity is the result of genetic defects in leptin, receptors of leptin, pro-opiomelanocortin (POMC), pro-hormone convertase-1, melanocortin-4 receptors (MC4), and ghrelin genes [80]. This evidence further supports PWS as the first and foremost genetic model for obesity and demonstrates leptin resistence as one of the primary causes of obesity. In PWS cases, leptin levels are increased causing an inability to produce an anorexigenic effect [80], whereas other studies have indicated hormonal and metabolic disorders that may be associated with hyperphagia including impaired growth hormone secretion and low insulin production [80-83]. People in the process of becoming addicted to food may have leptin resistance as well that leads to overeating [84]. An fMRI study showed that leptin could diminish food reward and enhance the response to satiety signals generated during food consumption through the modulation of neuronal activity in the striatum in leptin deficient human subjects [85], leptin also plays a role in regulating eating behavior partially via regulation of the DA pathway. The restriction of food increases circulating ghrelin released from the stomach and activates the mesolimbic system increasing DA release in the N_{AC}, while leptin and insulin inhibit them [79]. A study showed that food cues activated the brain regions involved in hedonic and incentive response when the healthy subjects were infused with ghrelin [86]. A positron emission tomography (PET) study showed that insulin resistance in the striatum and insula may require much higher levels of insulin to experience the reward and the interoceptive sensations of eating [87]. Thus, leptin and insulin can modify the DA pathway and change eating behavior. Leptin and insulin resistance in the brain DA pathways makes food intake a more potent reward and promotes palatable food intake [88]. Continuous stimulation of neuropeptide Y (NPY) receptors is the principal cause of hyperphagia [89]. An imbalance of NPY signaling at a local level (PVN and the arcade nucleus (ARC)) results in unregulated eating [46]. The neurotransmitter γ-aminobutyric acid (GABA) has also been known to enhance feeding behavior through its receptors or directly in the ARC. It can lead to decreased melanocortin signaling to the PVN, which in turn results in hyperphagia [90].

Solinas and Goldberg [91] studied how cannabinoid and opioid interaction affect the motivational aspects of food reinforcement, increased appetite and food consumption. Their findings showed that delta-9-tetrahydrocannabinol (THC) and morphine increased the reinforcement effects of food. Their study also confirmed that *mu* receptors were involved in the effects of THC and that cannabinoid 1 receptors were involved in the effects of morphine. Because of the high amount of endocannabinoide and opioid peptides located in the hypothalamus, THC and morphine have orexigenic effects that promote appetite and food consumption [92, 93]. These results indicated that THC and morphine not only responded to food stimuli, but also enhanced the palatable quantities of the food [94].

These central and peripheral signaling pathways are highly interconnected. Ghrelin stimulates dopaminergic reward pathways, while leptin and insulin inhibit these circuits. Moreover, signaling circuits in both the hypothalamus and the ARC receive peripheral signals that project to other regions of the brain, including midbrain dopaminergic centers [20].

HYPOTHALAMIC SIGNALING FOR APPETITE

The hypothalamus is a critical component in controlling appetite. It consists of the ventromedial hypothalamus (VMH), lateral hypothalamus (LH), dorsomedial nucleus (DMN) and PVN, and regulates feeding behavior and metabolism [89]. These sites receive appetite-stimulating impulses from referring organs and systems that are involved in nutrient and metabolite consumption and distribution, as well as in hyperphagia and obesity [95]. Ghrelin and leptin have been known to target the hyporhalamus in regulating feeding behavior. Leptin activates its receptors so that NPY, orexin (ORX), β-endorphin and α-melanocyte-stimulating hormones (MSH) can decrease appetite stimulation. The role of leptin and ghrelin feedback on the appetite regulating network (ARN) is crucial for maintaining homeostasis [96]. If there is a drop in leptin levels, the ARN is stimulated to release orexigenic NPY, agouti-related peptide (ArgrP) and GABA along with an inhibition of anorexigenic α-MSH [89]. If an animal consumes too many energy-laden calories and becomes inactive, then hyperleptinemia is promoted and fat accumulates in the body [89]. Hence, leptin transport and production in the hypothalamus is limited, and excess leptin circulation is unable to control appetite [97]. This may be an important factor to investigate in regard to food addiction and obesity.

The orexigenic and anorexigenic interactive pathways in the hypothalamus have critical roles in regulating appetite and craving. The ARN has appetite enhancing and reducing circuits that are located in the ARC-PVN axis of the hypothalamus, and it is affected by signaling from the LH and VMH [46]. These pathways may provide insight on the mechanisms underlying obesity and food addiction; because they have their components synthesized in the ARC and are targeted at the parvocellular PVN (pPVN) and magnocellular PVN (mPVN). The findings of Kalra [89] showed that if there was a disruption between the VMH and LH, then the affected individuals would overeat and gain weight. It indicated that the VMH is responsible for inhibiting signals to the ARC. On the other hand, certain areas in the LH which express ORX or melanin concentrating hormone (MCH) increase NPY release, thereby stimulating appetite. If there is nonstop stimulation of NPY receptors, then the satiety signal to the hypothalamus is inhibited resulting in continuous eating [89]. NPY levels rise in the ARC in order

to stimulate appetite during the absence or decrease of food intake. It has been shown that GABA can decrease melanocortin signaling to the PVN in order to stimulate appetite [90]. Overall, LH neurons that express ORX, MCH, and ARC neurons that coexpress NPY and GABA are the key components of the hypothalamus orexigenic pathway [46]. Manipulation of this pathway may provide novel insight for the treatment of food addiction as well as obesity in general. However, anorexigenic pathways are responsible for controlling the inhibition of appetite. The most important component in the melanocortin pathway is the ARC-PVN axis where POMC neurons coexpress α-MSH and cocaine- and amphetamine-regulating transcript (CART), that acts upon the PVN to curb appetite [89]. Another anorexigenic pathway consists of corticotrophin releasing hormone (CRH) neurons in the PVN, which release CRH due to stress to inhibit NPY-induced food intake [98]. Feeding regulation by anorexigenic neurochemical signals consists of the links between NPY and POMC and between NPY and CRH [94].

THE REWARD SYSTEM

In drug-related addiction, it has been shown that the ventral striatum and midbrain were associated with immediate rewards and that the hippocampus responded to reward consequences. The hippocampus is likely to reflect its involvement storing and retrieving the memories for the desired food [99]. It was also discovered that the globus pallidus, thalamus and subgenual cingulated were associated with immediate rewards, while the caudate, insula and ventral prefrontal cortex (vPFC) responded to reward consequences [100]. The mesolimbic reward system is a common pathway in response to food intake (consummatory food reward) [101], which may reinforce craving behavior and increase risk for overeating [18, 102, 103]. This is similar to the reinforcement sensitivity model of substance abuse, which postulates that certain people show greater reactivity of reward circuitry to psychoactive drugs [103]. Thus, reward processing is linked to addiction, and it is processed only if it can promote the craving of seeking food as a positive reward rather than facing the consequences of the reward behavior [96]. On the other hand, obesity is a "reward deficiency syndrome" [104] since DA D2 receptors are mediators of reinforcement and compulsiveness, and obese subjects were found to have lower levels of these receptors in the striatum [74]. In a study with subjects of normal weight, DA D2 availability in the striatum modulated eating behavioral patterns and DA D2 receptor availability negatively correlated with the tendency to eat when exposed to negative emotion [73]. Another hypothesis postulates that greater anticipated reward from food intake (anticipatory food reward) [101] increases the risk for overeating. Stice tested the hypothesis that obese individuals experience greater reward from food consumption (consummatory food reward) and anticipated consumption (anticipatory food reward) than lean individuals. Results suggested that individuals with increased activation in the gustatory cortex and somatosensory regions and decreased activation in the striatum in response to anticipation and consumption of food may be at risk for overeating and consequent weight gain [101]. In addition, Stice investigated the difference between emotional and nonemotional eaters during negative versus neutral mood states. Results indicated that emotional eating is related to increased anticipatory and consummatory food reward, but only during the negative mood state [101]. Most importantly, the common pathway for addiction involves the mesolimbic frontocortical dopamine (MFD) system, which is a reward pathway that controls eating behavior. Addictive behaviors cause the release of DA in the reward pathway causing almost immediate positive reinforcement [3]. Increased activation in the somatic parietal areas in food-addicted individuals suggests that enhanced activity in these regions involves sensory processing of food, which may make food even more rewarding [105, 106]. Morria and Dolan [106] showed that the state of hunger can influence the memory associated with food-related stimuli in fasting individuals. Joranby and colleagues [107] found that the localization of brain activation was dependent on the stimulus received. For example, the right anterior OFC had a variable response to all stimuli, despite hunger, while the right posterior OFC had different response only with food related stimuli during hunger. Thus, the posterior area was associated with general rewards, while the anterior part was associated with abstract and goal-oriented rewards.

FOOD CUES: INTERNAL AND EXTERNAL APPETITE TRIGGERS

In both developed and developing countries, people are constantly surrounded by food and motivational cues, which serve to enhance food consumption of not necessarily healthy foods [108, 109].

Certain brain networks are responsible for cue-induced eating and appetite induction. A specific food-associated environment to induce eating in healthy humans can shed light on why individuals became addicted to food overeat and obese. The predominant regions that have been associated with the drive to eat in both animal and human studies are the hypothalamus, striatum, OFC, insula, ACC, and AMY [110]; and brain regions consisting of the basolateral amygdala (BLA), LH and medial prefrontal cortex (mPFC) acting as a network to regulate eating by learned, motivational cues [45, 111, 112]. AMY has been shown to play a critical role in cue-enhanced eating [113], in appetite activation, and in maintaining a homeostatic balance [114-117]. When food-deprived individuals are shown food items compared to non-food items, greater activations of the AMY and medial orbitofrontal cortical area (mOFC) are observed [113, 117]. Visual cues for foods that have a higher incentive value produce greater activation in the AMY than foods that were recently eaten to satisfy hunger signals [114].

Normal eating signaling results from a response to decreased energy, but it can be triggered from environmental or learned cues, which in turn can alter the motivation for food consumption. Petrovich [118] found that neural connections between the BLA and LH are responsible for processing learned cues in order to forego the satiety signal and promote eating in satiated rats. The BLA shares anatomical connections with the hypothalamus in order to control feeding behavior [112]. A portion of the BLA that originates in the basolateral nucleus directly innervates the LH and sends vital projections to the LH, which together with the BLA forms part of the feeding circuit associated with the initiation of feeding [112]. The BLA-LH system is crucial for allowing learned cues to override satiety signals and stimulate eating during satiation. It is specifically associated with controlled eating via learned signals, because the system does not regulate baseline eating or the rate at which rats gain weight when fed *ad libitum*. This occurred primarily due to an associative process in which food ingestion was directed by a cue paired previously with food but not an unpaired one [109]. In a neurohormonal study, it may be plausible that potential feeding mechanisms involve direct glutamatergic connections from the BLA to LH, although the exact LH neurons involved in this process remain unidentified. Nevertheless, it may be safe to assume that BLA output could influence LH subsystems required for feeding initiation, and most importantly, the BLA-LH junction must be intact in order to initiate food cue-related eating [119]. Hunger caused by food cues is an adaptive mechanism for survival, and the learned cues can serve as a harmful force to promote overindulgence in food despite satiety, These particular learned cues can overcome specific satiety in order to promote continued eating [120].

Petrovich [109] investigated that cellular activation markers in the ventral medial PFC (vmPFC) neurons were activated following exposure to a newly-conditioned cue that stimulated eating in satiated rats. It caused impaired food consumption as a result of conditioned motivational cues when neurontoxic lesions were created in the vmPFC. Thus, the vmPFC plays a significant role in appetite influence by motivational cues. Interestingly, brain lesions did not

affect eating in the pretest baseline sessions or the rate at which rats gained weight when fed freely. However, lesions in the basolateral, basomedial and lateral nuclei of the AMY as well as the LH resulted in decreased food consumption and nonresponsiveness to appetite stimulation cues [121]. Given its important role in goal-oriented behavior, the orbital and medial prefrontal cortex (omPFC) could play a pivotal role in regulating the impulse to eat in response to highly appetitive cues in subjects with food addiction [122].

Metabolic factors and nonhomeostatic signals control motivational eating. Cravings for food in humans can be elicited by food cues and are often associated with hedonic overeating [123, 124]. Food craving is a learned appetite for energy through the reinforcing effects of eating a specific food when hungry [125]. Cue-induced eating could be considered binging, since it has been shown that sated rats consume more food pellets in a short period of time [109]. A human study [126] showed that food cues elicited specific cravings for the cued food, as opposed to a general desire to partake in undesired food in diet-restricted eaters. Most importantly, as the craving for the desire food increased, the restricted dieters consumed more of the cued food [126]. Lesions of the lateral OFC impair expectancy learning but not conditioned stimulus-potentiated feeding in rats [127]. Thus, the ventral areas within the rat vmPFC could represent a functional counterpart for the mOFC in humans [128]. DA also plays a critical role in food consumption stimulated by unpredictable cues [129]. DA efflux within the vmPFC resulting from signal-induced satiety was correlated with decreased consumption of high caloric, sweet and fatty foods; this may also be the case in PWS. Likewise, human OFC activation decreased in response to an olfactory cue of food eaten to satiety but not to an odor of uneaten food [122]. This observation may suggest a key point as to why obese individuals who are addicted to food continue to overeat despite satiety.

The environment in which food is consumed has been changing over the past 30 years in the United States. Increasingly disproportional food portions are served and eaten in restaurants and fast food places [130]. Advertising on television further elicits food cues encouraging even normal weight children and adults to seek out food despite lack of hunger signals. On the other hand, external food cues can be depicted in a much simpler fashion than the internal cues described above. In PWS patients, obsession and preoccupation with food, lack of satiation and incessant food seeking are typical behaviors as compared to normal obese humans [131, 132]. PWS adults show preference for sweet or high carbohydrate foods over any other type of food and often first eat the most desired foods, such as sweet, high caloric foods and will then eat the least preferred foods last. Since PWS cases are often highly affected by visual cues, even more so than normal obese adults, environmental cues are of much greater relevance. PWS patients will often have tantrums and aberrant behavior after seeing or smelling delicious, inviting food [133]. In PWS, the simple appearance of food cues (visual) has a very high emotional attachment and significance as opposed to those found in normal obesity that leads to bingeing episodes [134].

NEUROIMAGING STUDIES

Neuroimaging studies using PET and MRI have shown that aberrant eating behaviors and obesity have altered the brain function as well as neuroanatomy. In an fMRI study by Shapira [102], PWS patients showed much delayed blood oxygen level dependent (BOLD) response after glucose ingestion in the frontal cortex while viewing food pictures. Similar results in PWS adults showed an increased BOLD response in the vmPFC [43]. This data is best explained by the fact that PWS subjects have defects in the hypothalamus resulting in abnormal reward processing that leads to calorie overloading. It is well known in fMRI studies that the frontal cortex is involved in linking food and other rewarding objects with hedonism [122]. Wang *et al* found that when subjects viewed delicious food, the anterior insula and right OFC brain regions that are involved in the DA system were activated. FMRI studies have shown activation of the AMY with food-related stimuli, tastes and odor [103, 135, 136], and the activation response to gastric distention showed an association between activation in the AMY and subjective feeling of fullness [102, 137]. In two fMRI studies, Stice investigated striatal activation in response to receipt of chocolate milkshake versus a tasteless solution. The results suggested that individuals may overeat to compensate for a hypofunctioning dorsal striatum, particularly with genetic polymorphisms thought to attenuate dopamine signaling in this region [29]. A study by Smeets [103] showed that obese individuals experience greater reward from food consumption and anticipated consumption than lean subjects. This data indicated that individuals with greater activation in the gustatory cortex and somatosensory regions have a stronger response to anticipation and consumption of food, while weaker activation in the striatum may signal risk for overeating and consequent weight gain [101]. Another study by Stice *et al* tested the differences between emotional and nonemotional eaters response to food intake and anticipated food intake, and the results demonstrated that emotional eating is related to increase anticipatory and consummatory food reward during negative mood [138].

To test their hypothesis, Volkow [62] used PET and a multiple tracer approach to assess the DA system in the human brain in healthy controls as well as in subjects that are addicted to drugs and in those that are morbidly obese. The results of this study showed that the availability of DA D2 receptors in the striatum is shown to modulate the reinforcing responses to both drugs and food. Drugs and food compete for the reward pathway. The association with prefrontal metabolism suggests that decreases in DA D2 receptors in obese subjects contribute to overeating in part through deregulation of prefrontal regions implicated in inhibitory control and emotional regulation [62]. A human PET study with [^{11}C]raclopride measured DA release in the striatum after consumption of a favorite food showed that the amount of DA release was correlated with the ratings of meal pleasantness [60]. Several areas of the PFC including OFC and cingulated cortex (CG) have been implicated in food-related motivational behavior [139], and the mPFC involved in food craving [140, 141]. Volkow tested her hypothesis that food cues would increase extracellular DA in striatum and that these increases would predict the desire for food [65]. Using PET and [^{18}F]fluorodeoxyglucose (FDG) to measure regional brain glucose metabolism, Wang showed that morbidly obese subjects had a higher than normal baseline metabolism in the somatosensory cortex [67]. Taken together, these findings indicate that the brains of obese individuals may change in ways which not only reinforce food consumption but that also impair their ability to derive pleasure from activities other than eating.

PROPOSED PARADIGM

Food addiction is influenced by a complex regulatory system involving the integration of a wide variety of sensory inputs by multiple brain areas. Mesolimbic dopaminergic and opioid signaling pathways from the midbrain VTA and the N_{AC} play a key role in establishing these rewarding properties [142]. In addition, cognitive factors such as social environment, emotional state, or intentional efforts to control consumption can also influence food intake. Most of what we know about these regulatory systems derives from animal models, but our understanding of the control of eating behavior in humans is very limited.

Consistent with the biological imperative to identify and consume food, neuroimaging studies have begun to document the responsiveness of human brain to food cues such as odors and/or taste samples of food [29, 141], videos of people with food, photographs of food [85], and visual presentation of actual food [143]. Food cues have been contrasted directly with non-food stimuli [143] or

chosen to represent foods with high hedonic value and energy content [85].

FMRI is ideal for investigating the concerted activity among the ensemble of regions involved in a specific function, because scans can detect all regions of brain activation simultaneously. The temporal-spatial resolution and anatomical accuracy of fMRI techniques are now sufficient to allow a description of the properties of the major components in the CNS and most importantly, their functional interaction. In this case the dynamic activity of the brain reacting to visual stimuli can be monitored appropriately. Therefore, to elucidate the neural basis of obesity, we have proposed a method that measures brain response to visual food cues. Using fMRI, we can observe brain response to viewing photographs of food and non-food objects, and we looked specifically at brain regions important to the regulation of obese appetite and food intake. We propose to conduct an fMRI study to scan young healthy subjects of normal weight to measure different brain activation by visual images of highly rewarding-foods (such as high caloric food like hamburger, chips) compared with images of non-rewarding objects during various physiological states, in particular, we are interested in effects of fast food-branding on the brain and the effects in Chinese children with and without exposure to the Golden Arches (McDonald®) or the Kentucky Colonel (KFC®). The study tests the hypothesis of 'food addiction' that the fast food brands such as McDonald may have reinforcing effects in the brain and such effects may be related to children's drive to eat. Using the Chinese populations who have never been exposed to such food brands (as this CANNOT be done in the USA) as control, this study would have a strong impact in the areas of addiction and obesity.

Another research paradigm proposed is mostly based on a bottom-up approach to test the relationship between chronic subcutaneous recombinant leptin injections and weight loss [84]. In animal models, leptin sensitivity is positively correlated with the ability to resist dietary obese compared to those that have a tendency to remain lean on fattening diets. The fMRI techniques is a powerful tool to probe leptin neurological function in modulation of human ingestive behavior and ideal for investigating the concerted activity among the ensemble of regions involved in a specific function, because scans can detect all regions of brain activation simultaneously. Many recent studies have employed the fMRI techniques to gain neuroanatomical insights into the effects of leptin on the brain processing of hunger, satiety and food reward in obese human subjects [85, 144], in subjects with normal leptin production, and in subjects suffering congenital leptin deficiency in the presence or absence of chronic leptin supplement (4 to 52 weeks treatment). The results linked with brain regions that are also active to hunger (insula, parietal and temporal cortex) and to inhibition and satiety (prefrontal cortex) [85]. Other studies also showed that leptin responses to visual food stimuli differ in the obese versus lean subjects [145, 146] and differ before and after weight loss in obese subjects, but they also showed that leptin supplement can restore these leptin response altered with the lost pounds in weight-reduced individuals [146].

Therefore, we will conduct an fMRI study to help establish a diagnostic protocol susceptibility to diet-induced obesity in young, healthy humans of normal weight. We propose to assess the brain activation in response to acute subcutaneous leptin injection by examining the resting-state and exposure to stimuli consisting of food cues using an fMRI experiment. We will also attempt to correlate the fMRI leptin brain response with weight gain on a cafeteria diet. Positive results from this study will provide an invaluable diagnostic guideline for initiating early adulthood nutritional and behavioral intervention on an individualized basis to temper obesity development. This would constitute a realistic and meaningful cost-effective Obesity-Prevention strategy and will help curb rising obesity treatment-related health expenditures. Positive study outcomes will also highlight a technological breakthrough for fMRI investigation of region-specific neural activity in an acutely stimulated brain reactive state rather than in a chronically adapted state following long-term drug treatment or other types of intervention.

Thus, we hope to illuminate promising methods that use visual food cues to investigate mechanisms of human eating behavior, and to facilitate a more unified and reproducible approach to neuroimaging studies of food addiction and obesity. Results from this study can go far beyond obesity studies and could extend to the field of pharmacological research.

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