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Food addiction: A common neurobiological mechanism with drug abuse

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1. ABSTRACT

Drugs and food both exert a rewarding effect through the firing of dopamine neurons in the ventral tegmental area, resulting in the release of dopamine into the nucleus accumbens and effects on the mesolimbic pathway. Here, we review the neuroimaging literature to consider the validity of food addiction and the common neurobiological mechanisms that overlap in food and drug addiction. This review paper focuses on findings from Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI) and structural imaging studies, as well as evidence from neuroimaging studies of bariatric surgery and pharmacological interventions on obese individuals. We examine not only functional and structural changes in the mesolimbic pathways, but also in other frontal areas shown to be involved in drug addiction, including the prefrontal cortex, orbitofrontal cortex and anterior cingulate cortex, as well as changes in neurotransmitter systems beyond dopaminergic systems.

2. INTRODUCTION

Addiction is characterized by cycles of intoxication, withdrawal, and craving. As obesity and related metabolic diseases become increasingly common, it is important to examine determinants and consider evidence for the addictive properties of food. Both drug addiction and obesity result from repeated behaviors and habits that the individual has difficulty controlling despite awareness of undesirable consequences (1). Food consumption is rewarding, in part, through activation of the mesolimbic dopamine (DA) pathways. Certain foods, especially those high in sugar and fat, act in a similar way to drugs, leading to compulsive food consumption and loss-of-control over food intake (2). In addition, circuits of self-control and decision-making are impaired in obesity in a similar way to drug abuse and addiction due to dysregulation of prefrontal regions. The use of neuroimaging in investigating the mechanisms behind food addiction provides insight to the neurobiological correlates of this compulsive behavior,

and may help target therapeutic strategies through decreasing the rewarding properties of food, increasing alternative reinforcers of reward, and strengthening inhibitory control (1).

After an overview of food addiction, neurocircuitry and genetic and hormonal mechanisms, we will review the literature of Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) studies of obesity. Through the PET imaging literature, we present findings about numerous neurotransmitter systems, including DA, endogenous opioids, norepinephrine (NE), and serotonin (5-HT), as well as brain glucose metabolism. We review literature of functional MRI (fMRI), resting-state MRI (rsfMRI) and structural MRI including gray and white matter volumes, fractional anisotropy (FA) and mean diffusivity (MD). Last, we review the literature of brain changes in obese subjects following weight loss through bariatric surgery or pharmacological treatment with anti-craving medications.

We searched PubMed for clinical neuroimaging studies performed in both food-addicted and obese populations, and in populations of patients who received weight-loss treatment with bariatric surgery or medication. We acknowledge that obesity does not necessary imply a food addiction, and that food addiction can exist in lean subjects, however food addiction is likely to lead to excess calorie consumption and obesity. Obesity, as defined by a body mass index (BMI) greater than 30 kg/m^2, also proves to be simpler and more objective to measure than food addiction, and therefore it is more common to study obese populations than food-addicted populations. Food consumption is controlled by hypothalamic signaling and neuroendocrine hormones and neuropeptides that can also modulate reward mechanisms, as reviewed by Volkow *et al.* (2). The current review, however, focuses primarily on the neurotransmitters and neurocircuitry behind the reward of food consumption.

3. DEFINING FOOD ADDICTION

The concept of food addiction was first introduced into scientific literature by Randolph in 1956, who wrote of "a common pattern of symptoms descriptively similar to those of other addictive processes" observed in the consumption of foods such as corn, wheat, coffee, milk, eggs and potatoes (3). Since then, there has yet to be agreement on what is meant by the term food addiction. The term is not in the Diagnostic and Statistical Manual of Mental Disorders (*DSM*), the tool for diagnosing mental illness used by the American Psychiatric Association(APA) (4). The latest version, *DSM-5,* couches substance use disorders under the title "Substance-Related and Addictive Disorders" and is the first to include a behavioral addiction—gambling disorder, reflecting a growing understanding of the common underlying pathways of addictive processes. Still, whether or not the concept of food addiction represents another behavioral addiction such as gambling disorder, or whether elements of food, such as sugar, fat, or calories, have an inherently addictive quality similar to drugs of abuse continues to be debated (5, 6). These models are not mutually exclusive; food addiction is extremely complex and multidimensional. As the understanding of food addiction continues to evolve, it is likely that components from each of these major constructs are adopted by psychiatrists, psychologists and neuroscientist, which may help guiding treatment.

3.1. DSM substance use disorders and feeding and eating disorders

One of the earliest and more obvious ways to conceptualize food addiction is to compare it to the *DSM* criteria for substance use disorder (SUD) (7). The *DSM-5* combines the criteria for substance abuse and substance dependence under the term Substance Use Disorder (SUD). With this revision, a criterion for "craving" was added (4). The change echoes the development of a larger framework for addiction proposed by Koob *et al.,* wherein the last of the three major cycles of addiction includes a preoccupation and anticipation stage, marked by craving (8). Meule *et al* review the evidence for overlap between criteria for SUD and gambling disorders, and conclude that the current *DSM* criteria for substance use disorders serve as a better guide for future research (5).

The *DSM-5* is the first *DSM* version to include "Binge Eating Disorder" (BED). BED criteria include eating an amount of food larger than most people would eat in a discrete period and is associated with a loss of control over eating (4). This emphasis on escalated use and loss of control echoes the description of addiction put forth by Koob *et al.* of compulsive drug seeking (8). However, many researchers note that BED and bulimia nervosa do not appear to tell the full story of food addiction. For one, it may be too limiting in its criteria, requiring the loss of control to be associated with discrete episodes of overeating (9). Recent studies by Gearhardt *et al* indicate that less than half of individuals who meet criteria for BED also meet criteria for food addiction using the Yale Food Addiction Scale (discussed below); individuals who do meet criteria for both appear to have worsened pathology (9, 10).

3.2. Other diagnostic tools: Yale Food Addiction Scale and Addictions Neuroclinical Assessment

As interest in the idea of food addiction increased with the rise in obesity rates around the world, researchers sought a more precise way to capture the symptomology of food addiction. In 2009, Gearhardt *et al.* developed the Yale Food Addiction Scale (YFAS) for this purpose (11). This 25-item instrument

was developed with the substance dependence criteria from *DSM-IV* with additional items to assess the significance of distress or impairment caused by the symptoms. The YFAS demonstrated adequate internal reliability, good convergent validity with other measures of eating problems, and good discriminant validity as compared to distinct problems of alcohol consumption and impulsivity. It has recently been updated (YFAS Version 2.0.) to reflect the updated substance use disorder criteria in *DSM-5* (12).

While the YFAS is a tool that allows researchers to specifically examine food addiction, it is worth acknowledging emerging addiction frameworks that can be applied more broadly to any addictive process, including food addiction. The Addictions Neuroclinical Assessment (ANA) is a newer neuroscience-based framework of three clinically-oriented domains—incentive salience, negative emotionality, and executive function —that underlie the addiction cycle, discussed in more detail below (13). Importantly, ANA places less emphasis on any particular substance or addictive behavior, but seeks to understand the heterogeneity within and among addictive disorders (13).

3.3. Addiction neurocircuitry and food

For in-depth synopses of the state of science in the neurocircuitry of addiction, we refer to reviews by Koob and Volkow (8, 14). Reviewing evidence from animal models and neuroimaging, as well as studies of molecular and genetic targets within brain circuits associated with addiction, they characterize a heuristic framework of addiction. Like the ANA, this model focuses on the three functional domains of incentive salience, negative emotional states, and executive function, and the three corresponding neurobiological circuits: the basal ganglia, extended amygdala and prefrontal cortex, respectively. These domains underlie the three stages of addiction—binge/intoxication, withdrawal/negative affect and preoccupation/anticipation (craving)—that separate occasional, controlled use from the chronic, recurrent nature of addiction. More recent evidence further elaborates on the complexity of this model, accounting for neurotransmitter-defined mini circuits that can mediate functional neuroplasticity and affect each of the three major domains/stages, and can be targets for intervention (14).

The binge/intoxication stage involves the reward neurotransmitters of DA and opioid peptides in the nucleus accumbens (NAc) and dorsal striatum. Of note for the subject of food addiction, Barbano *et al.* have shown that the endogenous opioid systems are associated with the pleasure of food reward and have a synergistic effect with dopaminergic pathways to promote food intake (15). The withdrawal/negative affect stage engages activation of the extended amygdala, including the basal forebrain structures of the stria terminalis, central nucleus of the amygdala, and a transition zone in the medial part of the NAc. The preoccupation/anticipation stage engages the prefrontal cortex, hippocampus and insula (14). Both drugs of abuse and food activate the dopaminergic reward system described above in the binge/intoxication stage, but do so differently. Food stimuli modulate endogenous opioids and cannabinoids in this system as a function of palatability, as well as cause delayed increases of DA as a function of increased glucose and insulin. In contrast, drugs of abuse often increase DA through direct pharmacologic effects or, indirectly, through the opioid, nicotine, γ-aminobutyric acid (GABA) or cannabinoid systems (1, 16).

Thus, if either stimulus activates the reward system, there is potential for conditioned reinforcement in which previously neutral stimuli become paired with the rewarding stimuli and eventually become independent reinforcers of the behaviors associated with the reward. This well-established psychological phenomenon laid the groundwork for the concept of incentive salience, which has become a critical point of interest in addiction research. Incentive salience incorporates not only these learned associations but also an individual's physiological state into understanding motivation for rewards as a process driven by the mesocorticolimbic DA system (14). The concept has been of particular interest since it was demonstrated that midbrain dopaminergic neurons that initially fired in response to a novel reward transitioned to only firing in response to predictive stimuli or novel rewards, but not in response to rewards that had had sufficient repeated exposure (17, 18). The importance of incentive salience in the addiction process has been further reinforced in imaging studies, including studies involving cues of drugs of abuse and food, as discussed below.

3.4. Genetic mechanisms in addiction and obesity

The model of addiction neurocircuitry described above is now beginning to incorporate greater understanding and appreciation for genetic and epigenetic mechanisms that play a role in the development of addiction. The A1 allele for the dopamine D2 receptor (*Taq*1) has been associated with obesity and substance use disorders, which led Blum *et al* to develop the concept of 'Reward Deficiency Syndrome,' where genetic polymorphisms lead to abnormal behaviors (19).

At the same time, the relationship between the genetic components underlying these two chronic disease processes is certainly complicated and not yet clear. A recent 2016 genome-wide association study (GWAS) of 9,314 females of European ancestry who were identified as having food addiction by the modified YFAS did not identify a significant association with any single nucleotide polymorphisms (SNPs) or genes

implicated in drug addiction (20). However, a 2015 review of neurogenetic and neuroimaging evidence for a conceptual model of dopaminergic contributions to obesity found an array of evidence implicating a relationship between obesity and polymorphisms in DA receptors genes for DA receptors type 2, 3 and 4 (DRD2, DRD3, and DRD4) as well as the dopamine transporter (*DAT1*) and genes for enzymes associated with dopamine degradation—catechol-o-methyltransferase (*COMT*) and monoamine oxidase isomers A and B (21).

Further discussion of these relationships is beyond the scope of this review but given the evidence of high heritability of addiction and obesity (22, 23), as well as possible common underlying neurobiological pathways, this area is ripe for further investigation. As we incorporate pathways beyond the dopamine reward system (or binge/intoxication stage) in our model of addiction, we await exploration of possible implications with food addiction and obesity. For example, acknowledging the importance of the withdrawal/negative affect stage and the role of corticotropin-releasing factor (CRF) in this stage highlights the importance of the finding that SNPs in the receptor gene (CRHR1) are associated with heavy drinking, particularly in response to stressful life events (24, 25). To our knowledge, this kind of relationship has not yet been explored in the context of food addiction.

3.5. Hormonal mechanisms in addiction and obesity

As alluded to above, there is growing recognition of hormone dysregulation in the addiction cycle, adding yet another layer of complexity to these diseases. Disruption of the hypothalamic-pituitary-adrenal axis and CRF are indicated in the withdrawal/negative affect phase. During acute withdrawal from all drugs of abuse, CRF increases in the extended amygdala. There is some evidence that similar dysregulation of CRF may occur in relation to palatable foods. For instance, Cottone *et al.* demonstrated that rats, withdrawn from intermittent access to a high-sucrose, chocolate-flavored diet, showed increased anxiety-like behaviors, accompanied by increased mRNA and peptide expression of CRF in the central nucleus of the amygdala. Upon renewed access to the palatable food, overeating was noted (26). These findings were mitigated by pretreatment with the selective CRF_1 antagonist R121919 (26).

To focus on CRF dysregulation alone would be an oversimplification of the hormonal processes at play in both addiction and obesity. Food addiction in particular implicates several more hypothalamic neuropeptides involved in regulating food intake, such as leptin, insulin, ghrelin, orexin, cholecystokinin (CCK), peptide YY (PYY), and neuropeptide Y (NPY) (27–30). These hormonal systems have pathways connecting them to the dopaminergic reward system. Orexin is a neuropeptide secreted from the hypothalamus that regulates a range of physiological processes, including feeding, energy metabolism, and arousal. Recent evidence has pointed to a significant role of orexin, not only in feeding behavior dysregulation, but also recruitment of the orexin neuronal circuit by drugs of abuse, again pointing to overlap of reward processes even in the hormonal system (31).

4. PET IMAGING IN OBESITY AND FOOD ADDICTION

PET maps brain functioning by localizing and quantifying compounds of interest over time. Radioligands are selected to bind to receptors or proteins of interest in the brain so that their metabolism can provide insight into the functioning of studied brain regions. Several radiotracers relevant to the mapping of brain functioning in obesity are (^{11}C)raclopride, a relatively low affinity DRD2 antagonist, 2-deoxy-2(^{18}F) fluoro-D-glucose (FDG), a radio-labeled glucose-analogue molecule used to study regional metabolism of glucose in the brain, (^{11}C)carfentanil, a high affinity agonist for the μ-opioid receptor (MOR), (S,S)-(^{11}C) O-methylreboxetine (MRB), a radioligand that binds to the norepinephrine transporter (NET), and (^{18}F)altanserin, (^{11}C)SB20714, and (^{11}C)DASB, which bind to the serotonin 2A receptor ($5\text{-}HT_{2A}R$), 4 receptor ($5\text{-}HT_4R$) and transporter (5-HTT), respectively. Comparing the PET results from obese human subjects with substance use disorder subject allows us to compare the overlapping neurobiological correlates and evaluate the legitimacy of food addiction.

Studies using PET and (^{11}C)raclopride imaging on human subjects with alcohol, cocaine, heroin, and methamphetamine SUDs show that a defining trait of addiction is reduced DA release, as well as a decrease in the DRD2 availability in the NAc of the ventral striatum and in the dorsal striatum , resulting in a decreased neural response to reinforcers (32–34). With fewer DRD2 receptors available to respond to a decreased DA signal, there is less of a subjective rewarding perception from drug-induced DA release. It is speculated that compulsive disorders, including drug addiction and gambling, reflect a 'Reward Deficiency Syndrome' that is hypothesized to result from a reduction in the availability of DRD2 (35). To compensate for this deficiency of reward, drug users typically administer themselves larger quantities of the drug over a shorter period to experience the same reward effect.

The innate reinforcing nature of food is a result of DA release in the striatum (35). To determine whether an addiction to drugs is comparable to an addiction to food, studies examine DA release and availability of DRD2 in the brains of obese humans. A study

by Wang *et al.* revealed differences in DA release in response to caloric intake across varying BMIs. Subjects with higher BMIs showed less striatal DA release in response to consuming glucose than did subjects with lower BMIs, insinuating that excessive food intake could be a compensation for the difference between expected and actual response to food in obese subjects (36). Additional studies by Wang *et al.* have revealed reductions in striatal DRD2 availability correlated to increasing BMI (37). Furthermore, studies involving dopaminergic agonists and antagonists have demonstrated the role of DA signaling sensitivity in regulating food-seeking behavior. Patients undergoing treatment for schizophrenia with typical and atypical antipsychotics, which act by blocking DRD2, experienced an overall increase in body weight compared to those who were not treated with such antagonists (38). In contrast, studies involving patients receiving administrations of DA signaling amplifiers such as methylphenidate and amphetamine, which act by blocking DA transporters and releasing excessive DA respectively, showed that these drugs contribute toward weight loss (39). DA signaling in the brain is what appears to dictate the rewarding effects of food consumption, and whether calorific consumption is accompanied by addictive properties. Obese binge-eaters and individuals with substance use disorder share the commonality of a loss of control of their consumptions. The compulsive administration of food and drugs is reflected by poor DA signaling, suggesting that DRD2 may regulate compulsive behaviors. The lack of availability of DRD2 has been proposed to mandate the risk for developing compulsive behaviors related to a general addiction (35).

Further studies using PET with FDG indicate differences in regional brain glucose metabolism between healthy human controls and both compulsive drug users and obese binge-eaters. In both obese individuals and drug-addicted subjects, an association is seen between DRD2 availability and glucose metabolism in the orbitofrontal cortex and anterior cingulate gyrus of the prefrontal areas (40, 41). The impaired glucose metabolism of the prefrontal areas of the brain, which accompanies poor DA signaling in the striatum, appears to be responsible for the lack of inhibitory control seen in addicted individuals. The compulsivity resulting from poor functioning of these executive control centers compounds the lack of subjective reward from diminished DA sensitivity in the NAc.

Volkow *et al.*'s work has studied the association between DA signaling and prefrontal area functioning on subjects addicted to cocaine, methamphetamine, and alcohol. Using PET with (^{11}C)raclopride and FDG, Volkow has showed reductions in striatal D2 receptors in drug-addicted subjects that were associated with decreased metabolism in prefrontal cortical regions, when compared to healthy controls (40, 42, 43). Lower glucose metabolism in the executive control centers of prefrontal regions reflects their diminished functioning, resulting in loss of control over drug-taking behavior, despite awareness of negative effects (1). The downregulation of DRD2 and diminished DA sensitivity that adjunct drug addiction result in less downstream signaling to the prefrontal areas. The lack of DA-induced signaling to executive control centers results in less functional modulation of these regions, which explains the development of compulsivity that characterizes drug addiction (1).

Similarly, glucose metabolism of the prefrontal areas of the brain was shown to be correlated with the poor striatal DA signaling seen in obese individuals. The low striatal DRD2 availability seen in obese subjects may put these individuals at a higher risk for compulsive eating of calorie-rich foods due to the impaired ability of DA to modulate dorsolateral prefrontal cortex and medial prefrontal regions, which are known to play a role in executive function and inhibitory control. Striatal DRD2 availability was reduced in obese subjects and found to be correlated with (also reduced) metabolism in dorsolateral prefrontal, medial orbitofrontal, anterior cingulate gyrus, and somatosensory cortices, indicating that the behavioral changes in inhibitory control that appear as a result of chronic drug administration can also be observed in chronic food binging (41).

To elucidate whether diminished functioning of inhibition centers underlies compromised DA signaling pathways, or vice versa, Volkow *et al.* studied healthy subjects who were at a high risk for alcohol use disorder (AUD) due to family history, but were not alcoholics. FDG revealed normal levels of glucose metabolism in the orbitofrontal cortex, cingulate gyrus, and dorsolateral prefrontal cortex, while (^{11}C)raclopride revealed an augmented striatal DRD2 availability in subjects with a family history of alcoholism compared to healthy control subjects without familial vulnerability to alcohol addiction (44). Striatal DRD2 were associated with metabolism in prefrontal brain regions. However, higher striatal DRD2 levels were associated for a given level of metabolic activity in prefrontal regions in participants positive for family history of alcohol use disorder than in family negative participants. This finding suggests that prefrontal areas of the brain in which executive control has been mapped could underlie an individual's vulnerability to drug addiction. With the proper environment, stimuli, and access to substances, a vulnerable individual could fall victim to uncontrollable chronic drug administration, eventually causing an impairment of striatal DA signaling and further deregulating frontal areas which would thereby impair inhibitory control to a greater degree. Furthermore, it is postulated that higher levels of DRD2 could protect against addiction by enabling normal function of prefrontal regions involved in inhibitory control and

emotional regulation. Further research is necessary to understand if dopaminergic protection for maintenance of inhibitory control and emotional regulation is possible for those who may be predisposed to food addiction. Such a study would follow a similar procedure to that of Volkow *et al.* 2006, except it would have to recruit healthy controls with a family history of food addiction but who were not obese themselves. If these individuals showed normal prefrontal metabolism with higher than normal striatal DRD2 availability, it could be postulated that food addiction has a congenital component and could be protected by augmented DRD2 signaling. It is evident that an association exists between the ventral and dorsal striatum and prefrontal areas, and that congenitally compromised glucose metabolism of prefrontal areas could place a person at a higher risk for drug addiction due to an innate lack of inhibitory control. Diminished DA signaling because of compulsive drug administration could also result in a deregulation of prefrontal areas and of DRD2, further propagating the lack of control that characterizes the behavior of drug-addicted individuals. Whether this same scheme can be applied to food addiction is a question that requires additional research.

One major difference noted between drug addiction and food addiction is the change seen in the somatosensory cortex. Wang *et al.* show that obese individuals who had low striatal DRD2 availability (37) also had augmented glucose metabolism in the post-central gyrus in the left and right parietal cortex (45)(Wang, Volkow *et al*, 2002). These regions of the somatosensory cortex are associated with the subjective perception of taste. Given their enhanced activity in obese subjects, palatability is increased in these individuals, which further increases the reinforcing properties of food. The combination of reduced DRD2 signal and higher sensitivity to food's palatability could contribute toward the intense desire to consume calorific meals in a food addiction (35).

Substance use disorder and obesity both differ and share similarities regarding their regulation of MORs. In terms of substance use disorder, the nature of the drug will determine its effect on MORs. An association is seen between alcohol dependence and augmented MOR availability, as measured by (^{11}C) carfentanil binding, in the ventral striatum (46, 47). This may be a result of upregulation of MORs, or a reduction in endogenous opioids. Chronic cocaine administration shows increased MOR availability in the anterior cingulate and frontal cortex (48). Chronic opioid use is associated with MOR downregulation (49). It is plausible that direct MOR agonists like opioids mediate a downregulation in MORs, while indirect MOR agonists, like cocaine or alcohol, promote an upregulation in MORs. Karlsson *et al.* compared lean and obese human subjects' (^{11}C)carfentanil binding and found that obese individuals' MOR availability was significantly lower in brain regions of reward processing, including ventral striatum, insula, and thalamus (46). It is hypothesized that diminished MOR availability may promote overeating to compensate for a blunted MOR response. Interestingly, Karlsson *et al.* also compared (^{11}C)raclopride but found no difference between lean and obese subjects. Wang *et al.* (37) used subjects with a higher mean BMI, >50 kg/m^2, which suggests that changes in DRD2 availability may only be observed in a more pathological state.

Emotional eating (EE), a term used by researchers to indicate an increase in food consumption in response to negative emotions, is associated with obesity (50). It is postulated that deviations from normalized levels of norepinephrine (NE) contribute toward emotional eating seen in obesity. Dysfunction of the central NE system is linked to cognitive and mood disorders and stress responses, including overeating. Studies of the NE system have been performed across healthy control, addictive disorder, and obese populations. Ding *et al.* (51) analyzed PET imaging data with MRB for healthy controls and participants with cocaine dependence, and found significant upregulation of NE transporters (NET) in the thalamus of cocaine users. However, when Li *et al.* (52) compared PET imaging with MRB for healthy controls and morbidly obese subjects, a decrease in NET availability was found in the thalamus in obese subjects. This finding presents a notable difference in neurotransmission between individuals with substance use disorder and those with obesity. To investigate an association between NET availability in obese individuals and emotional eating Bresch *et al.* sought to measure EE through the EE subscale of the Dutch Eating Behavior Questionnaire for obese subjects and healthy controls before performing PET scans with MRB for these participants. This study did not find significant differences in EE scores and regional NET levels between healthy controls and obese participants. However, for obese individuals higher EE scores correlated with lower NET availability in the locus coeruleus and higher NET availability in the left thalamus (50). Collectively, these studies suggest that NE transmission is regionally impaired in substance use disorder, obese, and EE populations (50, 52). These results suggest that regional fluctuations in NET availability determine the deviations in motivated behavior, such as emotional eating, which are seen in substance use disorder and obesity. Additional studies are required to investigate whether the upregulation in NET for patients with cocaine use disorder (CUD) can be generalized to all SUDs.

The diversely functioning 5-HT system impacts feeding behaviors, known to signal satiety (53). A select few studies have used PET imaging with radioligands binding to serotonin receptors and transporters in healthy volunteers to study the relationship of receptor or transporter binding to BMI, as well as other

measures of compulsive behavior, alcohol consumption, and tobacco smoking. 5-HT_{2A}R availability was found to be positively correlated to BMI, while 5-HTT availability was found to be negatively correlated to BMI, but no correlations were found to alcohol and drug consumption (54, 55). Haahr *et al.* also found that BMI correlated to 5-HT_4R availability in the NAc, ventral pallidum, left hippocampal region, and OFC, but they did not collect measures of alcohol or drug consumption (53). More PET studies are needed to study the role of the serotonin system in drug and alcohol consumption.

5. MRI IMAGING IN OBESITY AND FOOD ADDICTION

Numerous functional and structural MRI studies have elucidated neurobiological correlates between drug addiction and obesity. Compared to healthy individuals, obese and drug addicted subjects show differences in reward and attention regions in response to cues and tasks as well as in a resting state. fMRI studies find that higher responsivity to food cues in reward and attention regions is predictive of future weight gain, and that weight gain is associated with altered reward region activity. Furthermore, studies using fMRI at resting state show connectivity differences in reward and prefrontal regions between obese and healthy weight individuals in the absence of cues or tasks. Lastly, studies using structural MRI show reductions in gray matter (GM) and white matter (WM) volumes in brain regions involved in executive function and inhibitory control.

fMRI imaging of alcohol, nicotine, cocaine and opioid substance use disorders have investigated brain activation in response to drug cue presentation. Drug cues have consistently produced activation of ventral striatum, amygdala, prefrontal cortex (PFC,) anterior cingulate cortex (ACC), orbitorfrontal cortex (OFC) and insula that are associated with relapse and treatment response measures (56). A similar response is seen in obese subjects to food-related cues. Rothemund *et al.* showed that obese subjects showed higher activation to high-calorie food visual cues in the ventral striatum when compared with controls, and that BMI predicted activation to high-calorie food cues in the dorsal striatum, anterior insula, claustrum, posterior cingulate, and postcentral and lateral OFC in obese subjects (57). Feldstein Ewing *et al.* investigated regions of activation following high- and low-calorie beverage consumption in obese/overweight adolescents. Greater activation was observed in the OFC , inferior frontal gyrus, NAc, and right amygdala in response to high vs. low-calorie beverages (58). They also investigated the relationship between biometrics, such as BMI and insulin resistance, and brain response to high and low calorie beverages. A positive correlation was observed between BMI and the blood-oxygen-level-dependent (BOLD) response to high vs. low-calorie contrast in the right post central gyrus and central operculum. Likewise, a positive correlation was observed between insulin resistance and activation to high vs. low-calorie contrast in bilateral/middle superior temporal gyrus, left OFC, and superior parietal lobe. However, it should be noted that no relationship was found between food addiction, as measured by the YFAS, and brain response (58). Tomasi *et al.* studied regions of overlap in the neural processing of food and drugs cues in 20 cocaine abusers (59). In comparing neutral cues to food and cocaine cues, they observed significant overlap among response to food and cocaine cues. Both food and cocaine cues produced an increased BOLD response in the cerebellum, OFC, inferior frontal and premotor cortices, and insula, as well as decreased response in the cuneus and default mode network (DMN). Upon comparison of activation between food cues vs. cocaine cues, cocaine cues produced lower activation in insula and post-central gyrus, and less deactivation in hypothalamus and DMN (59). Findings from these studies support the claim that there is significant, but not identical, neural overlap in response to food and drug cues among drug addicts and obese individuals, respectively.

Several fMRI studies have investigated the extent to which differences in reward and attention regions of the brain can predict future weight gain, and therefore be used as a measure of vulnerability for obesity. Based on literature showing obese/overweight individuals with an attentional bias to food cues, Yokum *et al.* sought to investigate whether an attentional bias to food cues could predict future weight gain (60). Thirty-five adolescent girls ranging from lean to obese were studied using fMRI and an attention network task with food and neutral cues. They found that BMI was predicted by greater lateral OFC activation to food cues, and observed a positive correlation between BMI and speed of behavioral response to both appetizing and unappetizing food stimuli, but not neutral stimuli. BMI also positively correlated with response in brain regions that are implicated in attention and reward, such as anterior insula/frontal operculum, lateral OFC, ventrolateral PFC, and superior parietal lobe during initial orientation to food cues (60). A later study also conducted by Yokum *et al.* found similar results, a positive correlation between activation of striatum, but not OFC, to food commercials vs. neutral commercials and BMI increase after a one-year follow-up (61). Another study intended to investigate neural vulnerability to obesity and weight gain used fMRI to measure response to receipt and anticipated receipt of palatable food, as well as monetary reward (62). Subjects had their body fat measured at the time of the scan and after a three-year follow up to determine if differences in neural processing of food, food cues, or monetary reward predicted future body

fat gain. They found that increased BOLD response in the OFC in response to cues anticipating milkshake receipt predicted future gains in body fat. Furthermore, responses to actual milkshake receipt and monetary reward were not predictive of future body fat gain (62). These findings suggest that individuals with higher responsivity in reward and attention regions of the brain in response to food cues are at greater risk of becoming overweight or obese.

Conversely, fMRI studies also show that gains in body weight and fat are associated with an increase in reward and attention relevant regions' responsivity to food cues. These findings draw parallels to how prolonged use of a drug of abuse enhances reward and attention relevant regions' responsivity to cues of that drug. Stice and Yokum conducted a repeated measures fMRI study to determine if gains in body fat are associated with greater reward and attention regions' responsivity to food cues (63). They measured brain activation upon impending milkshake receipt and milkshake receipt in healthy weight adolescents at baseline and after a two-to-three-year follow-up. Some participants gained body fat, some lost body fat, and others remained consistent. Increased brain activation was seen in the putamen, mid-insula, rolandic operculum, and precuneus in response to a cue signaling impending milkshake receipt in adolescents who gained body fat compared with those who showed stability or loss of body fat (63). However, it should be noted that this difference was partially driven by a reduction in BOLD response observed in subjects who remained stable in body fat after the 2–3 year follow up. Furthermore, there was a decrease in reward and attention region activation in response to actual milkshake receipt in subjects who gained body fat vs. those who remained consistent or lost body fat, suggesting that a prolonged period of overeating may increase responsivity to food cues in the striatum, and decrease reward region responsivity to actual receipt of food, similar to the actions of a prolonged period of drug taking (63).

Studies using resting state fMRI show differences in regional activity and connectivity independent of tasks or cues. One study by Hogencamp *et al.* investigated brain activity differences in reward regions between severely obese and normal weight females during resting state. They found that obese females showed increased activity in clusters located in the putamen, claustrum, and insula compared to normal weight females both before and after food intake (64). Another study by Wijngaarden *et al.* investigated the differences in regional connectivity at resting state between obese and lean subjects, and found several differences in regions of food reward and salience (65). At baseline, they observed connectivity between the left insula and hypothalamus was stronger in obese subjects, and connectivity between amygdala and ventromedial PFC was stronger in lean subjects. After a 48-hour fast, they observed increased connectivity between the hypothalamus and dorsal ACC in lean subjects, and decreased connectivity in obese subjects, suggesting that nutrient deprivation is processed differently in obesity (65).

Studies using structural MRI to investigate brain volume changes as a function of body weight reveal disruptions in regions of executive function in obese individuals. Yokum *et al.* used MRI to study adolescent females ranging from lean to obese (66). They found that obese women had less whole-brain GM volume than overweight and lean women, and that lower GM volumes in the superior frontal gyrus and middle frontal gyrus, areas implicated in inhibitory control, were associated with increases in BMI after a one-year follow-up (66). A review several years after this study echoed these results, reporting that numerous studies found higher levels of body fat to be associated with frontal GM atrophy, particularly in the PFC (67). These studies suggest that a loss of executive function and inhibitory control, a common theme in drug addiction, is likewise associated with obesity.

6. TREATING OBESITY AND FOOD ADDICTION

Treatments to aid in weight loss are becoming increasingly clinically relevant due to rising rates of obesity. Research shows that treatments can not only promote weight loss and body fat reduction, but can even change the way the brain responds to food. Based on the findings showing brain differences in obesity, researchers use neuroimaging to evaluate brain changes following weight loss therapy, leading to a better understanding of neural mechanisms in obesity and food addiction.

6.1. Neurobiological correlates of weight loss following bariatric surgery

Bariatric surgery is the most effective weight-loss therapy, associated with reduced mortality and improvements in co-morbid diseases (68). Pre-bariatric patients have a higher incidence of disordered eating behavior and binge eating than obese individuals pursuing a non-surgical weight loss treatment, including more frequent food cravings, higher eating disorder psychopathology and more depressive symptoms (69). Food addiction, as classified by YFAS, was found to be more prevalent in groups of pre-bariatric patients than obese individuals in other samples, and associated with more frequent food-cravings and higher attentional impulsivity (70). Following bariatric surgery, 93% of subjects who were identified with food addiction preoperatively no longer met criteria according to the YFAS (71). The extreme weight and behavioral changes that are associated with gastric bypass surgery is

a valuable way to study neurobiological correlates of food addiction, obesity, and weight-loss.

In both obesity and addiction, there is consistent evidence for reduced DRD2 availability in the striatum when compared to controls (37, 72) though there have been some discrepant findings in obesity (73) (46). A study by Steele *et al.* measured DRD2 availability before and after bariatric surgery in five female obese individuals using PET with (^{11}C)raclopride. In four out of five female subjects, DRD2 availability increased six weeks following bariatric surgery, suggesting that DRD2 availability increases in response to weight loss in mesolimbic pathways including the ventral striatum, caudate, and putamen (74). In patients who showed an increase in binding potential, the increase was roughly proportional to the amount of weight loss. Steele *et al.* hypothesize that overstimulation of DA receptors associated with obesity may lead to downregulation of dopamine release. However, Dunn *et al.* found an opposing result using the high affinity radioligand (^{18}F)fallypride, which, similar to (^{11}C) raclopride is an antagonist for DRD2 and additionally DRD3 (73). They found a decrease in (^{18}F)fallypride binding and DRD2 availability seven weeks following bariatric surgery, which could reflect increased extracellular dopamine levels that compete with (^{18}F)fallypride binding (73). Alternatively, it could be interpreted to refect a decrease in DRD2 levels following surgery. The discrepancy between the results of Steele *et al.* and Dunn *et al.* can be explained by a number of different factors, including younger participants and higher preoperative Beck's Depression Inventory (BDI) scores in Steele *et al.* (73). The studies both are also limited by small sample size of six or fewer participants. Yet another study found no significant change in DRD2 receptor availability in any brain region six weeks after bariatric surgery using single photon emission computed tomography (SPECT) and MRI (75). Although these studies yield promising results, further larger-sample studies are needed to understand the changes in the dopaminergic system following bariatric surgery.

With inconsistent patterns of DRD2 availability in obesity and bariatric surgery studies, PET studies have also assessed changes in the brain's MOR availability before and after bariatric surgery using (^{11}C)Carfentanil. Karlsson *et al.* studied 16 obese women eligible for bariatric surgery and 14 non-obese controls with both (^{11}C)raclopride and (^{11}C)Carfentanil and found that there were no differences in baseline DRD2 availability between the two groups (76). MOR availability, however, was lower preoperatively compared to controls in the ventral striatum, dorsal caudate, putamen, insula, amygdala, thalamus, OFC, and posterior cingulate cortex (76). After bariatric surgery MOR availability in the obese women increased in all but one subject 6 months to comparable levels to the controls, but there was no change in DRD2 availability postoperatively. Results of this study suggest that weight gain and excessive eating may over-stimulate the MOR system and lead to MOR downregulation. Similar results have been seen in studies of patients with opioid and alcohol use disorders. These patients all show recovery of MOR availability following detoxification and abstinence (77–79). Cocaine users also show normalization in MOR availability following detoxification, but chronic cocaine use is shown to increase, rather than decrease MOR availability (48). The changes in MOR availability following weight loss by bariatric surgery suggest that the MOR system is involved with food addiction and obesity, and is consistent with the efficacy of the combination therapy of the opioid antagonist naltrexone with buproprion for treating obesity (80).

In addition to the findings implicating the role of the dopaminergic and mu-opioid systems in food addiction and obesity, Haahr *et al* used the radiotracer (^{18}F)altanserin and(^{11}C)DASB to detect 5-HT_{2A} receptor (5-HT_{2A}R) and 5-HT transporter (5-HTT) availability respectably (81). Haahr *et al* found that neocortical 5-HT_{2A}R binding was greater in obese individuals than non-obese controls and that presurgical 5-HT_{2A}R binding predicted the size of weight loss following Roux-en-Y gastric bypass (RYGB) surgery and 5-HTT binding correlated with weight loss after RYGB (81). It's predicted that the increases in 5-HT_{2A}R availability reflects lower levels of 5-HT, which is associated with a higher appetite (82).

Reductions in neural responsivity assessed by fMRI have been shown in studies comparing pre- and post-RYGB surgery neural response to food cues in lingual gyrus, middle temporal gyrus, superior temporal gyrus, inferior parietal lobule and precuneus. A greater reduction of neural activity to high energy-dense food cues than to low energy-dense food cues was observed post-surgery, particularly in the ventral tegmental area (VTA), ventral striatum, putamen, posterior cingulate, and dorsomedial PFC (83). In another study, the insula, ventromedial PFC, and dorsolateral PFC all showed reduced neural responsivity to food cues one month following RYGB surgery. This effect was speculated to be related to postoperative changes in postprandial gut hormones such as $PYY_{3–36}$ and GLP-1 (84). Bruce *et al* found similar results, but additionally found increased activation to food versus nonfood pictures in the anterior PFC, an area associated with cognitive control (85). Another study found similar results using obese controls who were not trying to lose weight and found that the BOLD response in the VTA to high-calorie food cues declined significantly following bariatric surgery in RYGB participants compared to the weight-stable control participants at six months (86). Frank *et al.* suggested that

the brain activity differences observed after RYGB surgery may be reversing obesity-associated alterations, observing that in women who had undergone RYGB surgery longer than one year ago, there were no differences in brain activity to food and non-food cues compared to normal-weight controls, but obese women showed altered brain activity, including higher cerebellar and lower fusiform gyrus activity during visual cues (87). To elucidate whether the brain changes seen following bariatric surgery are unique to surgery or simply a result of weight loss, Bruce *et al* compared behavioral dieters and bariatric patients who were matched for amount of weight lost, and found that both groups had changed brain activations in response to food cues, but that the activation patterns differed. When hungry, diet weight loss participants had increased activation in the medial PFC and precuneus following weight loss, while bariatric patients had decreased activation in the medial PFC and precuneus (88).

RsfMRI studies have also shown changes in brain functional connectivity following bariatric surgery. such as For example, Lepping *et al* compared functional connectivity between behavioral dieters and patients undergoingpost-bariatric surgery and found that from pre-meal to post-meal, behavioral dieters showed increased connectivity between the precuneus/superior parietal lobe and the insula, while bariatric patients showed decreased connectivity between these regions (89). Increased connectivity between these areas may indicate greater awareness of feelings of fullness. Wiemerslage *et al.* also show decreased resting-state activity in putamen, insula, thalamus, caudate, cingulate cortex, and middle and inferior frontal gyri, which are associated with awareness of hunger and satiated bodily states (90).

Two 2016 studies evaluated whether bariatric surgery may normalize changes in GM and WM volume and recover reductions associated with obesity. Zhang *et al* compared structural abnormalities in the brain before and one month after laparoscopic sleeve surgery in obese subjects using fractional anisotropy (FA) and mean diffusivity (MD) as measures of WM integrity and directionality respectively, and gray and white matter densities (91). Obese subjects prior to surgery showed decreased GM and WM density in the caudate and putamen, which may signal abnormalities with responding to reward. One month following bariatric surgery, the obese subjects showed increased gray and white matter towards the level of the normal non-obese controls. BMI and YFAS ratings were negatively correlated with GM/WM densities and FA values, and positively correlated with MD values (91). Tuulari *et al* found that bariatric surgery led to a global increase in white matter density following initially lower white matter density than controls, and increase in grey matter density in the occipital and inferior temporal regions (92).

6.2. Neurobiological correlates of anti-craving medications in food addiction and obesity

The changes in food consumption that result with different psychoactive medications give information regarding the the roles of the dopaminergic, opioid, and cannabinoid neurotransmitter systems. A notable argument for the neurobiological similarity between food addiction/obesity and drug addiction is the efficacy of the anti-craving drugs naltrexone and buproprion in treating both food addiction and drug addictions. Naltrexone, currently used for treating alcohol and opioid dependence is an opioid antagonist with high affinity for the mu opioid receptor. Buproprion is a dopamine and norepinephrine inhibitor used to treat depression and as a smoking cessation aid. Naltrexone use has been shown to significantly reduce food intake in normal-weight volunteers and to reduce the subjective liking of foods, especially highly palatable foods (93). Naltrexone has also been shown to decrease reward activation in normal volunteers to seeing and tasting chocolate in the dorsal anterior cingulate and caudate, and to increase aversive-related activation in the amygdala and anterior insula after seeing and tasting moldy strawberry (94). Naltrexone alone, however, has shown mixed results in human weight loss trials, with studies (ranging from four-to-10 weeks of treatment) showing minimal or no weight loss compared to a placebo (95). The combination of naltrexone 32 mg with buproprion (NB32), however, was shown to reduce body weight by 5% or more after 56 weeks of treatment in 48% of obese participants in a multi-center, randomized, double-blind placebo-controlled phase 3 clinical trial (96). Wang *et al* studied the brain's reactivity to food cues in female obese patients before and after a four-week course of NB32.They found that NB32 attenuated activation in the hypothalamus to food cues and enhanced activation in the anterior cingulate, superior frontal gyrus, insula, superior parietal and hippocampal regions, areas of the brain involved in inhibitory control, internal awareness and memory (97).

The cannabinoid system has been shown to modulate brain reward signals to appetite and the consumption of food. The cannabinoid receptor 1 (CB1) antagonist, Rimonabant, was shown to promote weight-loss through reduced food consumption, and reduce activation of reward areas of the brain including ventral striatum and OFC following pleasant taste cues (98). Rimonobant was withdrawn from clinical use, however, because it presented depression- and anxiety-like side effects. Tetrahydrocannabivarin (THCv) is another CB1 antagonist that is currently investigated as a potentially safer alternative to Rimonobant for weight loss. Recent studies show that compared to placebo, THCv increases activation in the ACC, caudate, putamen and midbrain, reduces

functional connectivity of the default mode network, and increases functional connectivity between the left amygdala and dorsal ACC, part of the executive control network (99).

Other medications have been studied for treating obesity, including the FDA-approved combination of the sympathomimetic drug phentermine with the anticonvulsant drug topiramate, or the selective 5-HT_{2C} receptor agonist lorcaserin. It is currently thought that naltrexone with buproprion's effect of reducing craving is unique among weight-loss medications (80), but little research has been done on the neural effects of other centrally-acting weight-loss therapies and the mechanism of action in reducing appetite.

7. SUMMARY AND OUTLOOK

In summary, the findings of neuroimaging studies have advanced our understanding of neural mechanisms underlying obesity, and the commonalities with the neural mechanisms of alcohol and drug addiction. Summarizing these results supports the idea of food addiction as a construct, which may ultimately help the development of treatment plans for obesity and food addiction. Both food and drug addiction involve a dampening of DA signaling and downregulation of the MOR, coupled with impairment of prefrontal regions that are involved in inhibitory control. Despite the remarkable comparisons and differences between drug addiction and food addiction, it is important to note that treatment plans for food addiction and drug addiction also contain obvious differences: e.g., one can become totally abstinent from drugs to facilitate treatment, but it is not physiological feasible to completely abstain from food as a means of treatment. Therefore, measures other than pure abstinence must be considered when treating food addiction. In addition, the interaction between neurotransmitters and hormones in modulating feeding behaviors adds another level of complexity for future research to explore.

8. ACKNOWLEDGEMENT

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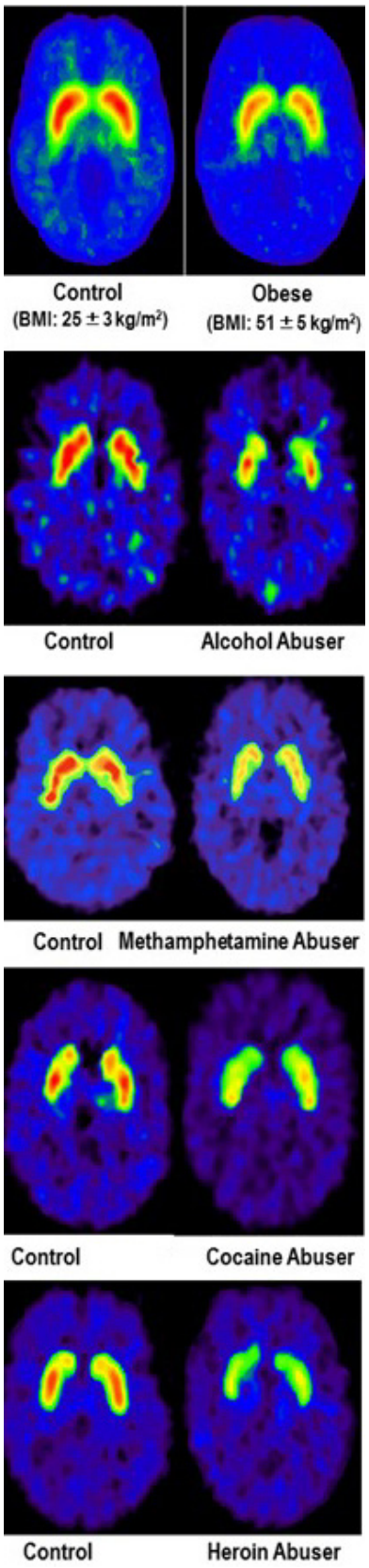

Figure 1. Decreased DRD2 availability in both obesity and substance use disorders. Adapted from Wang *et al.* 2001 (37).

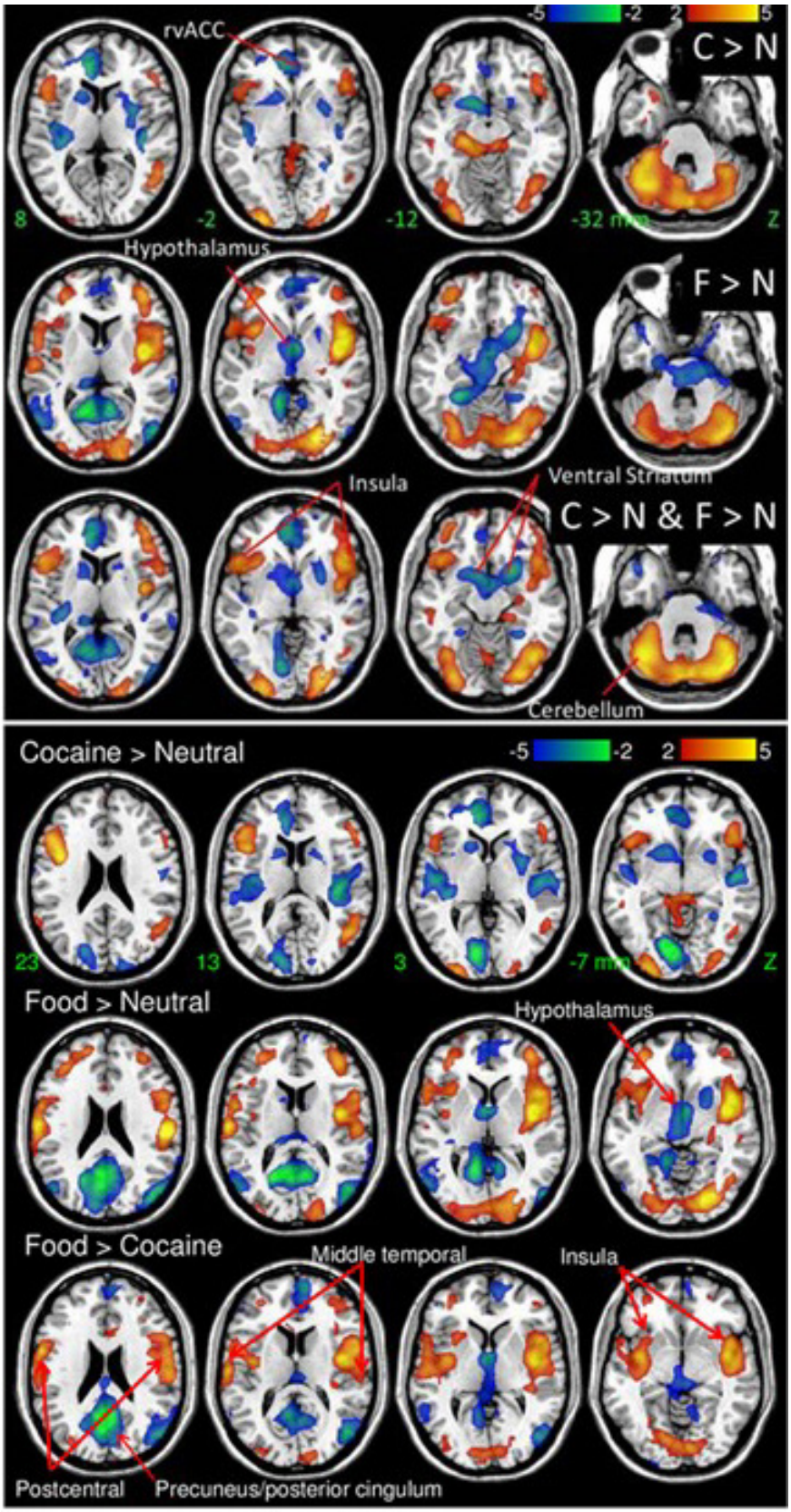

Figure 2. Overlapping activation to food and cocaine cues in patients with CUD. Adapted from Tomasi *et al.* 2015 (59).

Table 1. Neuroimaging studies related to obesity and food addiction

Authors (year)	Study group	Imaging task	Results
Glucose Metabolism			
Wang *et al.* (2002) (45)	N=10 obese subjects (BMI range 42–56) and N=20 non-obese controls	(^{18}F)-FDG PET	- The absolute global cerebral glucose metabolism in the obese subjects was similar to that in lean subjects - Obese subjects had significantly greater glucose metabolism in the bilateral parietal somatosensory cortex
Dopaminergic System			
Wang *et al.* (2014) (36)	*N*=19 healthy subjects (BMI range 21–35)	(^{11}C)raclopride PET after consumption of artificial sweetener and glucose	- The amount dopamine levels changed in the ventral striatum following calorie intake was correlated to subject BMI - In normal weight individuals (BMI <25), consumption of calories was associated with increases in dopamine in the ventral striatum - In obese individuals, calorie consumption was associated with decreases in dopamine in the ventral striatum
Volkow *et al.* (2006) (44)	N=15 non-alcoholic subjects with familial history of alcoholism and N=16 healthy controls without familial history of alcoholism	(^{11}C)raclopride PET and (^{18}F)-FDG PET	- DRD2 availability was higher in non-alcoholic members with familial history of alcoholism than in healthy controls without familial history of alcoholism, supporting the hypothesis that high levels of D2 receptors may protect against alcoholism - DRD2 availability was associated with metabolism in ACC, OFC and PFC, and with scores of positive emotionality on a personality measure
Volkow *et al.* (1993) (40)	N=20 patients with CUD and N=38 healthy controls	(^{18}F)NMS PET and (^{18}F)-FDG PET	- When compared to normal controls, cocaine abusers had decreases in DRD2 availability that were associated with decreased metabolism in frontal regions, most markedly OFC and ACC
Volkow *et al.* (2008) (41)	*N*=10 obese subjects (BMI range 46–56) and N=12 non-obese controls	(^{11}C)raclopride PET and (^{18}F)-FDG PET	- In obese subjects striatal DRD2 availability was lower than controls and was positively correlated with metabolism in dorsolateral PFC, medial OFC, ACC and somatosensory cortex - No significant correlations with prefrontal metabolism in non-obese controls
Wang *et al.* (2001) (37)	*N*=10 obese subjects (BMI range 42–60) and N=10 non-obese controls	(^{11}C)raclopride PET	- The availability of DRD2 was decreased in obese individuals compared to controls - DRD2 availability correlated negatively with BMI in obese subjects
Steele *et al.* (2010) (74)	N=5 female obese subjects (BMI range 41–53) approved for RYGB bariatric surgery	(^{11}C)raclopride PET pre-surgery and 6 weeks post-surgery	- DRD2 availability increased 6 weeks post-surgery, roughly proportional to the amount of weight lost, especially in the ventral striatum, caudate and putamen
Dunn *et al.* (2010) (73)	N=5 female obese subjects (BMI range 38–54) approved for RYGB or VSG bariatric surgery	(^{18}F)-fallypride PET pre-surgery and 6–11 weeks post-surgery	- DRD2 availability decreased post-surgery in caudate, putamen, ventral striatum, hypothalamus, substantia nigra, and medial thalamus
de Weijer *et al.* (2014) (75)	N=19 female obese subjects (BMI range 39–61) approved for RYGB bariatric surgery	(123I)iodobenzamide SPECT pre-surgery and 6 weeks post-surgery	- No significant changes in striatal DRD2 receptor availability
Opioid System			
Weerts *et al.* (2011) (47)	N=25 patients with AUD and N=30 healthy controls	(^{11}C)carfentanil PET on day 5 of alcohol abstinence	- Patients with AUD showed increased MOR availability in the ventral striatum when compared to healthy controls

Gorelick *et al.* (2005) (48)	N=17 patients with CUD and N=16 healthy controls	(^{11}C)carfentanil PET over 12 weeks of cocaine abstinence	- Patients with CUD showed increased MOR availability in ACC and frontal cortex after 1 and 12 weeks of abstinence - Increased MOR availability was associated with self-reported cocaine craving and cocaine use severity before admission
Heinz *et al.* (2005) (78)	N=25 patients with AUD and N=10 healthy controls	(^{11}C)carfentanil PET over 5 weeks of alcohol abstinence	- Abstinent alcoholic patients displayed an increase in MOR availability in the ventral striatum, including the , which correlated with the severity of alcohol craving - After 5 weeks, MOR levels remained elevated in the 12 patients that were reassessed
Zubieta *et al.* (2000) (77)	N=3 opioid-dependent subjects and N=3 healthy controls	(^{11}C)carfentanil PET over 32 days of varying buprenorphine doses then following 8 days of abstinence	- MOR availability in heroin users was significantly increased in inferofrontal cortex and ACC during abstinence when compared to controls
Karlsson *et al.* (2015) (46)	N=13 obese subjects (BMI range 37–49) and N=14 healthy controls	(^{11}C)carfentanil PET	- Obese individuals have significantly lower MOR availability when compared to controls
Karlsson *et al.* (2016) (76)	N=16 obese subjects approved for bariatric surgery (BMI range 36–40) and N=14 non-obese controls	(^{11}C)carfentanil and ^{11}C) raclopride PET pre-surgery and 6 months post-surgery	- Before surgery, obese subjects initially had lower MOR availability when compared to controls - After surgery, diminished food intake resulted in an increase of MOR availability for obese subjects to a level comparable to controls - No changes in D2 receptor availability in obese subjects post-operatively
Noradrenergic System			
Ding *et al.* (2010) (51)	N=10 cocaine- and N=12 healthy controls	(^{11}C)MRB PET	- There is a significant upregulation of NET in thalamus and dorsomedial thalamic nucleus in individuals with CUD when compared to controls
Bresch *et al.* (2016) (50)	N=10 obese subjects (BMI range 39–46) and N=10 healthy controls	(^{11}C)MRB PET and Emotional Eating (EE) subscale of the Dutch Eating Behavior Questionnaire	- Obese individuals and controls did not significantly differ regarding EE scores and regional NET availability. For obese individuals only, a higher degree of EE correlated to lower NET availability in the locus coeruleus and to higher NET availability in the left thalamus
Li *et al.* (2014) (52)	N=17 obese subjects (BMI range 32–36) and N=17 healthy controls	(^{11}C)MRB PET	- There is a significant downregulation of NET in the thalamus, including the pulvinar, in obese individuals when compared to controls
Serotonergic (5-hydroxytryptamin, 5-HT) System			
Erritzoe *et al.* (2009) (54)	N=136 healthy volunteers, 14 of whom were obese (BMI mean 25.2.±4.3.)	(^{18}F)-altanserin PET	- Cerebral cortex 5-HT$_{2A}$ receptor (5-HT$_{2A}$R) binding correlated positively with BMI - Alcohol consumption and tobacco smoking were not correlated with 5-HT$_{2A}$R binding
Erritzoe *et al.* (2010) (55)	N=60 healthy volunteers, 6 of whom were obese (BMI mean 26.5.±5.9.)	(^{11}C)DASB PET	- 5-HTT binding negatively correlated with BMI - Alcohol consumption and tobacco smoking were not correlated with 5-HTT binding
Haahr *et al.* (2012) (53)	N=28 healthy volunteers, 12 of whom were overweight or obese (BMI mean 26.5.±6.8.)	(11C)SB207145 PET	- 5-HT$_4$R binding correlated with BMI in NAc, ventral pallidum, left hippocampal region and OFC
Haahr *et al.* (2015) (81)	N=21 obese subjects (BMI mean 40.1.±4.1.) and N=10 healthy controls	(^{18}F)-altanserin PET and (^{11}C) DASB PET	- Higher presurgical 5-HT$_{2A}$R binding predicted greater postsurgical weight loss, although presurgical 5-HTT binding did not - Postsurgical weight loss was correlated with the change in both 5-HT$_{2A}$R and 5-HTT binding - 5-HT$_{2A}$R and 5-HTT downregulation were associated with greater weight loss

Neural responsivity (fMRI)			
Tomasi *et al.* (2015) (59)	N= 20 individuals with CUD	Cue reactivity with food, and cocaine, and neutral visual cues (4T fMRI) and (^{11}C)raclopride PET	- Cocaine and food cues activate similar, but not identical, pathways - Both cocaine and food cues increased activation in cerebellum, insula, OFC, inferior frontal and premotor cortices, and decreased activation in cuneus, DMN, ventral striatum, and hypothalamus compared to neutral cues - fMRI signals were proportional to striatal DRD2 availability
Rothemund *et al.* (2007) (57)	N=13 obese females and 13 normal-weight females	Cue reactivity with high-calorie food, low-calorie food, and neutral visual cues	- Obese subjects showed higher activation in the dorsal striatum than controls to high-calorie food cues - BMI predicted activation in the dorsal striatum, anterior insula, claustrum, posterior cingulate, and postcentral and lateral OFC to high-calorie cues in obese subjects
Feldstein Ewing *et al.* (2016) (58)	N=24 overweight/obese adolescent subjects (BMI range 25.7.-45.6.2)	Cue reactivity with high vs. low calorie beverage gustatory cues (3T fMRI)	- Significantly greater BOLD response observed in OFC, inferior frontal gyrus, NAc, and right amygdala upon comparison of high>low colorie contrast
Yokum *et al.* (2011) (60)	N=35 adolescent females (BMI range 17.3.-38.8.)	Attention network task with food and neutral visual cues (3T fMRI)	- BMI positively correlated with speed of behavioral response to food cues as well as activation of brain regions related to attention and reward, including anterior insula, OFC, ventrolateral PFC, and superior parietal lobe - Increased activity in the lateral OFC to appetizing food cues predicted future increases in BMI
Yokum *et al.* (2014) (61)	N=30 adolescents (BMI mean 26.9.2±5.4.3)	Cue reactivity with food and neutral television commercials (3T fMRI)	- Positive correlation observed between striatal activation in response to food commercials relative to neutral commercials and change in BMI over a one-year follow-up
Stice *et al.* (2015) (62)	N=153 healthy weight adolescents (BMI mean 20.8.±1.9.)	fMRI- brain activation measured in response to receipt and anticipated receipt of milkshake or glass of water, and 3-year follow-up	- Greater activation in the OFC in response to anticipated milkshake receipt predicted future body fat gain
Stice and Yokum (2016) (63)	N=162 healthy weight adolescents (BMI mean 20.8.±1.9.)	fMRI- brain activation measured in response to receipt and anticipated receipt of milkshake or glass of water, and 2-year and 3-year follow-up	- Adolescents who showed a >3% increase in body fat after 2-year follow-up showed increased striatal responsivity in putamen, insula, and precuneus to cues signaling impending milkshake receipt, and decreased striatal responsivity to milkshake receipt compared with those who maintained or lost body fat
Ochner *et al.* (2011) (83)	N=10 female obese subjects approved for RYGB bariatric surgery (BMI range 40–54)	Cue reactivity with high and low calorie food, and neutral visual and auditory cues, 1 month pre- and 1 month post-surgery (1.5.T fMRI)	- Greater postsurgical reductions in whole-brain activation to high than low calorie foods especially in VTA, ventral striatum, putamen, posterior cingulate, dorsomedial PFC - No significant differences in activation to high-calorie or low-calorie food cues post-surgically
Ochner *et al.* (2012) (84)	N=5 female obese subjects approved for RYGB bariatric surgery (BMI range 39.1.-48.1.)	Cue reactivity with high and low calorie food visual and auditory cues in fasted and fed states, 1 month pre- and 1 month post-surgery (1.5.T fMRI)	- Postsurgical reductions in neural responsivity to food cues in the fasted, but not fed state, in the insula, ventromedial PFC and dorsolateral PFC - Preoperative differences in neural activation during the fasted and fed states in the precuneus, no significant differences in neural activation in the fasted
Bruce *et al.* (2012) (85)	N=10 obese subjects approved for LAGB bariatric surgery (BMI range 35–45)	Cue reactivity with visual food and non-food cues in fasted and fed states, pre- and 12 weeks post-surgery (3T fMRI)	- Postsurgical reductions in brain activation to food vs. non-food cues in parahippocampus, insula, medial PFC, and inferior frontal gyrus - Postsurgical increases in activation to food vs. non-food cues in anterior PFC

Faulconbridge *et al.* (2016) (86)	N=22 female obese subjects approved for RYGB bariatric surgery (BMI mean 44.6.±4.3.), 18 female obese subjects approved for VSG bariatric surgery (BMI mean 43.9.±4.1.), N=19 female obese weight-stable controls (BMI mean 43.3.±4.4.)	Cue reactivity with HC food and LC food visual cues, pre- and 6 months post-surgery (3T fMRI)	- Postsurgical reduction in brain activation in the VTA to HC vs. LC food cues in RYGB subjects - Changes in fasting ghrelin was correlated to changes in VTA activation in both RYGB and VSG subjects
Bruce *et al.* (2014) (88)	N=15 obese subjects approved for LAGB bariatric surgery (BMI range 30–45) and 16 obese participants approved for behavioral diet intervention	Cue reactivity with food and non-food cues in fasted and fed states pre-and 12 weeks post-surgery or post-diet intervention (3T fMRI)	- Behavioral dieters showed increased activation in left precuneus and right medial PFC in the fasted state after weight loss when compared to bariatric patients - Bariatric patients showed increased activation in bilateral temporal cortex in the fed state after weight loss compared to behavioral dieters
Frank *et al.* (2014) (87)	N=11 obese women (BMI mean 40.2.±0.8.) 9 previously obese women who had undergone RYGB bariatric surgery (BMI mean 27.1.±0.9.) and 11 normal weight controls (BMI 21.4.±0.5.)	Cue reactivity with high and low calorie food, and non-food visual cues (1.5.T fMRI)	- Obese subjects showed higher activation than the other groups in the cerebellum and lower activation in the fusiform gyrus - Obese subjects showed higher activation than the other groups in the hypothalamus in low compared to high calorie food cues - Obese subjects showed higher activation than the other groups in hippocampus and cerebellum during a working memory task - Obese subjects showed higher functional connectivity than the other groups in frontal regions - No difference in brain activity between normal weight and RYGB subjects during cue reactivity or resting state
Ness *et al.* (2014) (100)	N=19 obese subjects approved for LAGB bariatric surgery (BMI mean 41.9.8±3.0.8)	Cue-reactivity with food and non-food visual cues in fasted and fed states pre-surgery (3T fMRI)	- Greater activation in fasted state to food cues in left temporal gyrus, left middle temporal gyrus and middle frontal gyrus associated with greater weight loss 6 months post-surgery - Greater activation to food cues in fed state in bilateral posterior cingulate cortex associated with greater weight-loss 6 months post-surgery
Goldman *et al.* (2013) (101)	N=31 subjects at least 1 year post-RYGB gastric bypass surgery (BMI 32.1.6–18.2.8 divided into N=24 “more successful,” and N=7 “less successful” groups	Food craving/resisting task with food and non-food visual cues (3T fMRI)	- More successful bariatric surgery patients, who lost 50% or more excess body weight, had significantly more activation in the dorsolateral prefrontal cortex when instructed to resist visual food cues (dorsolateral PFC)
Wang *et al.* (2014) (97)	N=40 obese females (BMI mean 32.5.±3.9.)	Cue reactivity with food and non-food video cues, before and after 4 weeks of escalated-dose naltrexone (32 mg) and buproprion (360 mg) (NB32) or placebo treatment (4T fMRI)	- After treatment, participants taking NB32 had higher activation to food cues in anterior, middle, and posterior cingulum, superior frontal and middle temporal cortices, superior parietal cortex, and posterior insula, and decreased activation in the hypothalamus than at baseline - Placebo group had lower activation in anterior, middle, and posterior cingulum, superior frontal and superior parietal cortices, hippocampus and parahippocampus after 4 weeks
Murray *et al.* (2014) (94)	N=20 non-obese healthy volunteers (BMI 23.0.9±1.8.0)	Cue reactivity with rewarding (chocolate) and aversive (moldy strawberry) food taste and visual cues following single dose of naltrexone (50 mg) or placebo (3T fMRI)	- Naltrexone decreased activation in the dorsal ACC to chocolate cues and increased activation in the amygdala and interior insula to moldy strawberry cues
Horder *et al.* (2010) (98)	22 non-obese healthy volunteers	Cue-reactivity with rewarding (chocolate) and aversive (moldy strawberry) food taste and visual cues, following 7 days of rimonabant (20 mg) or placebo treatment (3T fMRI)	- Subjects receiving rimonabant showed less activation to visual chocolate cues in the right ventral striatum/putamen and mid orbitofrontal cortex and taste and visual moldy strawberry cues in the caudate and left ventral striatum, and greater activation in the lateral OFC

Resting-state MRI			
Wijngaarden *et al.* (2015) (65)	N=13 obese subjects (BMI mean 35.4.±1.2.) and N=11 lean subjects (BMI mean 23.2.±0.5.)	Resting state scans performed at baseline (after an overnight fast) and after a prolonged 48-hour fast	- Stronger connectivity between left insula and hypothalamus at baseline in obese subjects compared to lean subjects - Stronger connectivity between amygdala and ventromedial PFC at baseline in lean subjects compared to obese subjects - After fasting, connectivity between hypothalamus and dorsal ACC increased in lean subjects and decreased in obese subjects
Hogenkamp *et al.* (2016) (64)	N=17 obese females (BMI mean 42.3.±4.8.) and N=12 normal-weight females (BMI mean 22.7.±1.8.)	Resting state scans performed before and after food intake	- Obese females had increased activity in putamen, claustrum, and insula compared with normal weight females - No changes in group differences after food intake
Lepping *et al.* (2015) (89)	N=15 obese subjects approved for LAGB bariatric surgery (BMI mean 41.3.5±1.9.7) and N=13 obese subjects approved for behavioral diet intervention (BMI mean 40.1.0±1.8.0)	Resting state scans in fasted and fed states 3 months post-surgery or post-diet intervention (3T fMRI)	- Behavioral dieters showed greater functional connectivity between the left precuneus/ superior parietal lobule and the insula after eating - Bariatric patients showed decreased functional connectivity between precuneus/ superior parietal lobule and insula after eating
Wiemerslage *et al.* (2016) (90)	N=11 obese females approved for bariatric surgery (BMI mean 40.8.±4.0.)	Resting state scans in fasted and fed states pre- and 3 months post-surgery (3T fMRI)	- Post-surgery, subjects showed decreased brain activity in the insula, putamen, thalamus, caudate, ACC, and middle and IFG.
Rzepa *et al.* (2015) (99)	N=19 non-obese healthy volunteers (BMI range 19–26)	Resting state scan following single dose of THCv (10 mg) and placebo (crossover design)	- After THCv dose, decreased resting state functional connectivity between amygdala and default mode network, and increased resting state functional connectivity between the amygdala and dorsal ACC and between the dorsomedial PFC and IFG compared to placebo - BMI was positively correlated with functional connectivity between the amygdala and precuneus under the placebo, but not THCv condition
Structural MRI			
Willette and Kapogiannis (2015) (67)	Review of 44 articles from 2004–2013	MRI studies investigating the relationship between adiposity and GM and WM volumes	- Higher levels of body fat associated with frontal GM volume, particularly in the PFC - Global and regional WM volume showed variable association with adiposity, DTI measures show higher levels of body fat to be associated with decreased WM microstructural integrity
Yokum *et al.* (2012) (66)	N=83 young females (BMI range 17.3.-38.9.)	Structural images, 1-year follow-up (3T MRI)	- Obese females had less total GM and WM volume than overweight and lean females - Reduced WM volumes in middle temporal gyrus, fusiform gyrus, parahippocampal gyrus, and dorsal striatum correlated with BMI - Reduced GM volumes in superior frontal gyrus and middle frontal gyrus were associated with increase in BMI over a 1-year follow up
Zhang *et al.* (2016) (91)	N=15 obese patients approved for LSG bariatric surgery (BMI mean 38.1.0±1.5.0) and 18 normal weight controls (BMI mean 21.6.0±0.7.0)	Structural and diffusion-weighted images pre- and 1 month post-surgery (3T MRI)	- DTI measures show decreased WM integrity and directionality in pre-surgery obese subjects than controls in the left anterior corona radiata, corpus callosum, fornix and saggital stratum, which increased post-surgery - Decreased GM density in pre-surgery obese subjects than controls in IFG and SFG, rostral ACC, dorsomedial PFC, and temporal lobe, which increased post-surgery - Decreased WM density in pre-surgery obese subjects than controls in caudate, thalamus, right IFG, rostral ACC, middle cingulate cortex, postcentral gyrus and precuneus, which increased post-surgery

Tuulari *et al.* (2016) (92)	N=47 obese patients approved for gastric bypass or sleeve gastrectomy surgery (BMI range 35–53) and 29 non-obese controls (BMI range 17.8.-29.9.)	Structural images pre- and 6 months post-surgery (1.5.T MRI)	- Decreased GM density in inferior orbitofrontal, frontal, temporal, cerebellar, and occipital regions and insula in obese subjects pre-surgery - Decreased WM density in OFC and midbrain/ medulla in obese patients pre-surgery - BMI, waist circumference, body fat percentage, systolic blood pressure, fasting glucose and plasma lipids were negatively associated with GM and WM density, while plasma HDL cholesterol levels were positively associated with GM and WM volumes - Increased GM density in obese patients post-surgery in occipital and temporal cortical regions, weight loss was associated with increases in GM in frontotemporal cortex, insula, right thalamus and cerebellum - Increased WM density globally in obese patients post-surgery, weight loss was associated with increases in WM in posterior temporal cortex, precentral and superior frontal cortex

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Abbreviations (Table): 5-HT_{2A}R: serotonin receptor 2A, 5-HTT: serotonin transporter, ACC: anterior cingulate cortex, AUD: alcohol use disorder, BMI: body-mass index, CUD: cocaine use disorder, DMN: default mode network, DRD2: Dopamine D2 receptor, DTI: diffusion tensor imaging, EE: emotional eating, fMRI: functional magnetic resonance imaging, IFG: inferior frontal gyrus, GM: gray matter, LAGB: laparoscopic adjustable gastric banding, LSG: laparoscopic sleeve gastrectomy, NET: norepinephrine transporter, OFC: orbitofrontal cortex, OUD: opiate use disorder, MOR: mu-opioid receptor, MRI: magnetic resonance imaging, MRS: magnetic resonance spectroscopy, NAc: nucleus accumbens, NET: Norepinephrine transporter, PET: positron emission tomography, PFC: prefrontal cortex, RYGB: Roux-en-Y gastric bypass SPECT: single-photon emission computed tomography, SFG: superior frontal gyrus, THCv: tetrahydrocan-nabivarin, VSG: vertical sleeve gastrectomy, VTA: ventral tegmental area, WM: white matter

Abbreviations (Text): PET: positron emission tomography, MRI: magnetic resonance imaging, fMRI: functional magnetic resonance imaging, DA: dopamine, NE: norepinephrine, 5-HT: serotonin, rsfMRI: resting-state functional magnetic resonance imaging, FA: fractional anisotropy, MD: mean diffusivity, BMI: body mass index, DSM: Diagnostic and Statistical Manual of Mental Disorders, APA: American Psychological Association, BED: binge eating disorder, YFAS: Yale Food Addiction Scale, ANA: Addictions Neuroclinical Assessment, NAc: nucleus accumbens, GABA: γ-aminobutyric acid, SNP: single nucleotide polymorphism, DRD2: dopamine 2 receptor, DRD3: dopamine 3 receptor, DRD4: dopamine 4 receptor, CRF: corticotropin-releasing factor, CCK: cholecystokinin, PYY: peptide YY, NPY: neuropeptide Y, FDG: 2-deoxy-2(18F)fluoro-D-glucose, MOR: mu-opioid receptor, MRB: 2-deoxy-2(18F)fluoro-D-glucose, 5-HT_{2A}R: serotonin 2A receptor, 5-HT_4R: serotonin 4 receptor, 5-HTT: serotonin transporter, NET: norepinephrine transporter, AUD: alcohol use disorder, EE: emotional eating, CUD: cocaine use disorder, GM: gray matter, WM: white matter, PFC: prefrontal cortex, ACC: anterior cingulate cortex, OFC: orbitofrontal cortex, BOLD: blood oxygen level-dependent, DMN: default mode network, BDI: Beck's Depression Inventory, SPECT: single photon emission computed tomography, NB32: naltrexone 32 mg with buproprion, CB1: cannabinoid receptor 1, THCv: tetrahydrocannabivarin, 5-HT_{2C}R: serotonin 2C receptor

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