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Relation of Obesity to Consummatory and Anticipatory Food Reward

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Abstract

This report reviews findings from studies that have investigated whether abnormalities in reward from food intake and anticipated food intake increase risk for obesity. Self-report and behavioral data suggest that obese relative to lean individuals show elevated anticipatory and consumatory food reward. Brain imaging studies suggest that obese relative to lean individuals show greater activation of the gustatory cortex (insula/frontal operculum) and oral somatosensory regions (parietal operculum and Rolandic operculum) in response to anticipated intake and consumption of palatable foods. Yet, data also suggest that obese relative to lean individuals show less activation in the dorsal striatum in response to consumption of palatable foods and reduced striatal D2 dopamine receptor density. Emerging prospective data also suggest that abnormal activation in these brain regions increases risk for future weight gain and that genotypes associated with lowered dopamine signaling amplify these predictive effects. Results imply that individuals who show greater activation in the gustatory cortex and somatosensory regions in response to anticipation and consumption of food, but who show weaker activation in the striatum during food intake, may be at risk for overeating, particularly those at genetic risk for lowered dopamine receptor signaling.

Keywords

Obesity; anticipatory and consummatory food reward; neuroimaging review

Obesity is associated with increased risk for mortality, atherosclerotic cerebrovascular disease, coronary heart disease, colorectal cancer, hyperlipidemia, hypertension, gallbladder disease, and diabetes mellitus, resulting in over 111,000 deaths annually in the US [1]. Currently, 65% adults and 31% of adolescents in the US are overweight or obese [2]. Unfortunately, the treatment of choice for obesity (behavior weight loss treatment) only results in moderate and

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transient reduction in body weight [3] and most obesity prevention programs do not reduce risk for future weight gain [4]. The limited success of these interventions may be due to an incomplete understanding of the factors that increase risk for obesity. Although twin studies imply that biological factors play a key etiologic role in obesity, few prospective studies have identified biological factors that increase risk for future weight gain.

Reward from Food Intake

Theorists have posited that obesity results from abnormalities in reward processing. However, the findings seem somewhat inconsistent, which has prompted competing models regarding the relation of abnormalities in reward processing to the etiology of obesity. Some researchers propose that a hyper-responsiveness of reward circuitry to food intake increases risk for overeating [5,6]. This is similar to the reinforcement sensitivity model of substance abuse, which posits that certain people show greater reactivity of brain reward systems to reinforcing drugs [6]. Others hypothesize that obese individuals show hypo-responsiveness of reward circuitry, which leads them to overeat to compensate for this deficiency [7,8]. This Reward Deficiency Syndrome may contribute to other motivated behaviors, including substance abuse and gambling [9].

Consistent with the hyper-responsiveness model, obese individuals rate high-fat and high-sugar foods as more pleasant and consume more of such foods than lean individuals [10,11,12]. Children at risk for obesity by virtue of parental obesity prefer the taste of high-fat foods and show a more avid feeding style than children of lean parents [13,14,15]. Preferences for high-fat and high-sugar foods predict elevated weight gain and increased risk for obesity [16,17]. Obese versus lean individuals report that food intake is more reinforcing [18,19,20]. Self-report measures of general sensitivity to reward correlate positively with overeating and body mass [21,22].

Brain imaging studies have identified regions that appear to encode subjective reward from food consumption. Consumption of palatable foods, relative to consumption of unpalatable foods or tasteless foods, results in greater activation of the right lateral orbitofrontal cortex (OFC), frontal operculum and insula [23,24]. Consumption of palatable food also results in dopamine release in the dorsal striatum [25]. Microdialysis studies in rodents indicate that appetitive tastes also release dopamine in the nucleus accumbens shell and core, as well as the prefrontal cortex [26,27]. Animal studies indicate that bingeing on sugar increases extracellular dopamine in the nucleus accumbens shell [28]. Stimulation of the meso-limbic network using a μ-opioid receptor agonist [29] and lesions of the baslolateral amygdalar and lateral hypothalamus circuit can produce overeating [30], supporting the importance of this region's neurochemistry in food consumption.

Accumulating data implicate deficiencies in dopamine receptors in obesity. Obese relative to lean rats show less D2 receptor density in the hypothalamus [31] and in the striatum [32] and reduced hypothalamic dopamine activity when fasting, but release more phasic statewise dopamine when eating and do not stop eating in response to insulin and glucose administration [33]. Obesity-prone Sprague-Dawley rats have reduced dopamine turnover in the hypothalamus compared to the diet-resistant strain before they become obese and only develop obesity when given a palatable high-energy diet [34,35]. D2 receptor blockade causes obese but not lean rats to overeat [31,36], suggesting that blockade of already low D2 receptor availability may sensitize obese rats to food [37]. Obese versus lean humans show reduced striatal D2 receptor density [38,39]. When exposed to the same high-fat diet, mice with lower D2 receptor density in the putamen show more weight gain than mice with higher D2 receptor density in this region [40]. Dopamine antagonists increase appetite, energy intake, and weight

gain, whereas dopamine agonists reduce energy intake and produce weight loss [41,42,43, 44].

Studies in neuroeconomics indicate that activation in several areas of the brain correlate positively with the size of the monetary reward and reward size [45]. Similar findings have emerged for food reward [46]. Moreover, such responses vary with hunger and satiety. Responses to food taste in the midbrain, insula, dorsal striatum, subcallosal cingulate, dorsolateral prefrontal cortex, and dorsal medial prefrontal cortex are stronger in a fasting versus a sated state, presumably reflecting the greater reward value of food induced by deprivation [47,48]. Such data suggest that responses to food in several brain regions can be used as an index of reward responsivity.

Although few brain imaging studies have compared lean and obese individuals using paradigms that assess activation of reward circuitry, certain findings align with the thesis that obese individuals show hyper-responsiveness in brain regions implicated in food reward. A Positron Emission Tomography (PET) study found that obese relative to lean adults showed greater resting metabolic activity in the oral somatosensory cortex, a region that encodes sensation in the mouth, lips, and tongue [8], prompting the authors to speculate that enhanced activity in this region may render obese individuals more sensitive to the rewarding properties of food and increase risk for overeating, though this has not been directly confirmed. Extending these findings, a functional magnetic resonance imaging (fMRI) study conducted by our lab to examine the neural response of obese and lean adolescents to a primary reward (food) found that obese versus lean adolescents showed greater activation in the oral somatosensory cortex in response to receipt of chocolate milkshake versus receipt of tasteless solution [49]. These data collectively suggest that obese relative to lean individuals have an enhanced neural architecture in this region. Future research should use voxel-based morphometry to test whether obese individuals show higher grey matter density or volume in this region relative to lean individuals.

Studies using PET found that the mid dorsal insula, midbrain, and posterior hippocampus remain abnormally responsive to consumption of food in previously obese individuals compared to lean individuals [50,51], prompting those authors to speculate that these abnormal responses may increase risk for obesity. Our lab has found that obese relative to lean adolescents show greater activation of the anterior insula/frontal operculum in response to food consumption [49]. The insular cortex has been implicated in a variety of functions related to the integration of autonomic, behavioral, and emotional responses [51]. Specifically, the human neuroimaging literature suggests that the insular cortex has anatomically distinct regions that sustain different functions regarding taste processing [52–55]. Mid insula has found to respond to perceived intensity of a taste irrespective of affective valuation, while valence-specific responses are observed in anterior insula/frontal operculum [54]. Interestingly obese versus lean individuals show increased activation in both regions during consumption of food, suggesting that they may perceive greater taste intensity as well as experience increased reward.

Animal research also implicates a hyper-responsiveness of the dopamine target regions in obesity. Specifically, Yang and Meguid [56] found that obese rats show more release of dopamine in the hypothalamus during feeding than do lean rats. However, to date no PET imaging study has tested whether obese humans showed greater dopamine release in response to food intake relative to lean humans.

Other findings stand in contrast to models of hyper-responsiveness and instead are consistent with the hypothesis that obese individuals show hypo-responsivity of reward circuitry. Obese relative to lean rodents show less striatal D2 receptor binding [32]. PET studies likewise find that obese relative to lean humans show less striatal D2 receptor binding [38,39], leading these

authors to speculate that obese individuals experience less subjective reward from food intake because they have fewer D2 receptors and lower DA signal transduction. This is an intriguing hypothesis, though a few caveats warrant attention. First, the proposed inverse relation between D2 receptor availability and subjective reward from food intake is difficult to reconcile with the finding that humans with lower D2 receptor availability report greater subjective reward from methylphenidate than humans with more D2 receptors [57]. If reduced striatal D2 receptors availability produces attenuated subjective reward, it is unclear why individuals with lower D2 binding report that psychostimulants are more subjectively rewarding. Resolving this apparent paradox would advance our understanding of the relation between dopamine action and obesity. Methodological issues also warrant attention in interpreting the PET literature on D2 receptors. First, D2 receptors play both a post-synaptic and a pre-synaptic autoregulatory role. Whereas it is generally assumed that PET measures of D2 binding in the striatum are driven by post-synaptic receptors, the precise contribution of pre and post- synaptic signaling is uncertain, and lowered pre-synaptic receptor levels would have the opposite effect of fewer post-synaptic receptors. Second, because benzamide based PET ligands compete with endogenous dopamine, the finding of lowered D2 receptor availability, could arise due to increased tonic dopamine activity [58]. Yet, even though binding potential is modulated by endogenous DA, the correlation between D2 receptor binding in the normal and a dopamine depleted state is extremely high, which suggests that a larger proportion of the variance in D2 binding is due to creptor density and affinity, rather than differences in endogenous DA levels [59]. Another argument against greater tonic dopamine levels in the striatum of obese individuals emerges from data from rodents. Obese rats have decreased basal dopamine levels in the nucleus accumbens and decreased stimulated dopamine release in both the nucleus accumbens and dorsal striatum [60].

Additional animal research links reduced D2 functioning with weight gain. As noted, D2 receptor blockade causes obese but not lean rats to overeat [31,33] suggesting that blockade of already low D2 receptor availability may sensitize obese rats to food [61]. When exposed to the same high-fat diet, mice with lower D2 receptor density in the putamen show more weight gain than mice with higher D2 receptor density in this region [40]. Dopamine antagonists increase appetite, energy intake, and weight gain, whereas dopamine agonists reduce energy intake and produce weight loss [41,42,43,44]. Taken together these data suggest that D2 functioning is not simply a consequence of obesity, but rather increases risk for future weight gain.

Brain imaging data likewise suggest that obesity is associated with a hypo-responsive striatum. In two fMRI studies conducted by our lab, we found that obese versus lean adolescents show less activation in the dorsal striatum in response to food consumption [49,62]. Because we measured BOLD response, we can only speculate that the effects reflect lower D2 receptor density. This interpretation seems reasonable because the presence of the Taq1A A1 allele, which has been associated with reduced dopaminergic signaling in several post mortem and PET studies [63–67], significantly moderated the observed BOLD effects. That is, activation in this region showed a strong inverse relation to concurrent Body Mass Index (BMI) for those with the Taq1A A1 allele, and a weaker relation to BMI for those without this allele [49]. Yet, the blunted striatal activation may also implicate altered dopamine release from food intake rather than a lower D2 receptor density. Accordingly, it will be important to investigate DA release in response to food intake in obese versus lean individuals. The above findings echo evidence that addictive behaviors such as alcohol, nicotine, marijuana, cocaine, and heroin abuse are associated with low expression of D2 receptors and blunted sensitivity of reward circuitry to drugs and financial reward [68,69,70]. Wang and associates [8] posit that deficits in D2 receptors may predispose individuals to use psychoactive drugs or overeat to boost a sluggish dopamine reward system. As noted, a PET study found evidence that lower striatal D2 receptor availability among non-addicted humans was associated with greater self-reported

liking in response to methylphenidate [57]. Further, lower D2 receptor availability in the striatum is associated with lower resting metabolism in the prefrontal cortex, which may increase risk for overeating because this latter region has been implicated in inhibitory control [38].

An alternative interpretation of the above findings is that consumption of a high-fat, high-sugar diet leads to down-regulation of D2 receptors [25], paralleling neural response to chronic use of psychoactive drugs [57]. Animal studies suggest that repeated intake of sweet and fatty foods results in down-regulation of post-synaptic D2 receptors, increased D1 receptor binding, and decreased D2 sensitivity and μ-opioid receptor binding [71,72,73]; changes that also occur in response to chronic substance abuse. Interestingly, there is also experimental evidence that increased intake of high-fat foods leads to greater taste preferences for high-fat foods: rats assigned to a high-fat maintenance diet preferred high-fat foods over high-carbohydrates foods, relative to control animals fed a moderate-fat diet or a high-carbohydrate diet [74,75]. These data imply that increased intake of an unhealthy high-fat food results in a preference for that same food type. Accordingly, a priority for research is to test whether abnormalities in brain reward circuitry predate obesity onset and increase risk for future weight gain.

We recently tested whether the degree of activation of the dorsal striatum in response to receipt of a palatable food during an fMRI scan correlated with an increased risk for future weight gain [49]. Although the degree of activation of target brain regions did not show a main effect in predicting weight gain, the relation between abnormal dorsal striatum activation in response to food receipt and weight gain over the subsequent 1-year period was moderated by the A1 allele of the *TaqIA* gene, which is associated with lower levels of striatal D2 receptors (see section on genotypes that impact dopamine signaling below). Lower striatal activation in response to food receipt increased risk for future weight gain for those with the A1 allele of the *TaqIA* gene. Interestingly, data suggest that for individuals without the A1 allele, a hyper-responsiveness of the striatum to food receipt predicted weight gain (Fig 1). However, this latter effect was weaker than the strong inverse relation between the striatal response and weight gain in individuals with the A1 allele.

In sum, extant data suggest that obese relative to lean individuals show a hyper-responsive gustatory cortex and somatosensory cortex in response to food receipt, but that obese individuals also show hypo-responsiveness in the dorsal striatum in response to food intake relative to lean individuals. Thus, extant findings do not accord with a simple hyper-responsivity model or a simple hypo-responsivity model of obesity. A key priority for future research will be to reconcile these seemingly incompatible findings that appear to suggest that obese individuals show both hyper-responsivity and hypo-responsivity of brain regions implicated in food reward relative to lean individuals. As noted, it is possible that chronic intake of high-fat and high-sugar foods, which may result because of the hyper-responsitivity of the gustatory and somatosensory cortices, leads to down-regulation of striatal D2 receptors and the blunted response in this region to intake of palatable foods. Another possibility is that the curtailed reactivity of the dorsal striatum and reduced D2 receptor availability are a product of elevated tonic dopamine among obese relative to lean individuals, which reduces D2 receptor availability and responsivity of dopamine target regions such as the dorsal striatum in response to food receipt. Prospective studies that test whether the hyper-responsivity in the gustatory and somatosensory cortices and hypo-responsivity of the dorsal striatum increases risk for obesity onset should help distinguish abnormalities that are vulnerability factors for unhealthy weight gain versus consequences of a history of overeating or elevated body fat. To date, only one prospective study has tested whether abnormalities in brain regions implicated in food reward increase risk for future weight gain [49]. Another priority for future research will be to determine whether obese individuals show elevated sensitivity to reward in general or only elevated sensitivity to food reward. The evidence that receipt of food, alcohol, nicotine, and

money activate similar regions of the brain [23,76,77] and that abnormalities in reward circuitry are associated with obesity, alcoholism, drug abuse, and gambling [9] suggests that obese individuals may show greater sensitivity to reward in general. Yet, it is difficult to draw conclusions because these studies did not assess sensitivity to both general reward and food reward. Obese individuals may show elevated sensitivity to general reward, but even greater sensitivity to food reward.

Anticipated Reward from Food Intake

The literature on reward makes an important distinction between appetitive and consummatory reward, or wanting versus liking [78]. This distinction may be critical for resolving some of the seeming discrepancy between hyper- and hypo- responsivity to food stimuli. Some theorists have hypothesized that the core issue in obesity relates to the anticipatory phase, with greater anticipated reward from food increasing the risk for overeating and obesity [79,80]. Incentive salience theory posits that consummatory and anticipatory reward processes operate in tandem in determining the reinforcement value of food, but that over repeated presentations of food, the hedonic value (liking) decreases, while anticipatory reward increases [81]. Jansen [82] proposed that cues such as the sight and smell of food eventually elicit physiological responses that trigger food craving, increasing risk for further overeating after conditioning.

Imaging studies have identified regions that appear to encode anticipatory food reward in humans. Anticipated receipt of a palatable food, versus unpalatable food or a tasteless food, activates the OFC, amygdala, cingulate gyrus, striatum (caudate nucleus and putamen), dopamine midbrain, parahippocampal gyrus, and fusiform gyrus in men and women [23,79].

Two studies have directly compared activation in response to consumption and anticipated consumption of food to isolate regions that show greater activation in response to one phase of food reward versus the other. Anticipation of a pleasant taste, versus actual taste, resulted in greater activation in the dopaminergic midbrain, ventral striatum, and the posterior right amygdala [23]. Anticipation of a pleasant drink resulted in greater activation in the amygdala and mediodorsal thalamus, whereas the receipt of the drink resulted in greater activation in the left insula/operculum [83]. These studies suggest that the amygdala, midbrain, ventral striatum, and mediodorsal thalamus are more responsive to anticipated consumption of food, whereas the frontal operculum/insula is more responsive to the consumption of food. Anticipation and receipt of money, alcohol, and nicotine also activate somewhat distinct regions that correspond to those that are implicated in anticipatory and consummatory food reward [76,84,85,86].

The ventral striatum and insula show greater activation in response to viewing images of high calorie versus low calorie foods [87,88], implying that activation in these regions is a response to the greater motivational salience of high-calorie foods. Responses to food images in the amygdala, parahippocampal gyrus, and anterior fusiform gyrus were stronger while fasting, verse sated [89], and responses to food images in the brainstem, parahippocampal gyrus, culmen, globus pallidus, middle temporal gyrus, inferior frontal gyrus, middle frontal gyrus, and lingual gyrus were stronger after 10% weight loss relative to initial overweight [90], presumably reflecting the greater reward value of food induced by deprivation. Increases in self-reported hunger in response to presentation of food cues were positively correlated with greater activation of the OFC, insula, and hypothalamus/thalamus [91,92,93]. Transcranial magnetic stimulation of the prefrontal cortex attenuates food craving [94], providing further evidence of the role of the prefrontal cortex in anticipatory food reward. Stimulation of this area also reduces urges to smoke and smoking [94], implying that the prefrontal cortex plays a broader role in anticipated reward.

A critical feature of reward coding shifts from food intake to anticipated food intake after conditioning. Naïve monkeys that had not received food in a particular setting showed

activation of dopamine neurons only in response to food taste; however, after conditioning, dopaminergic activity began to precede reward delivery and eventually maximal activity was elicited by the conditioned stimuli that predicted the impending reward rather than by actual food receipt [95,96]. Kiyatkin and Gratton [97] found that the greatest dopaminergic activation occurred in an anticipatory fashion as rats approached and pressed a bar that produced food reward and activation actually decreases as the rat received and ate the food. Blackburn [98] found that dopamine activity was greater in the nucleus accumbens of rats after presentation of a conditioned stimulus that usually signaled food receipt than after delivery of an unexpected meal. These data do not argue against models of phasic dopamine firing that emphasize the role of dopamine in signaling positive prediction errors [99], but rather emphasize the importance of dopamine in the preparation for, and anticipation of food reward.

A history of elevated sugar intake may contribute to abnormal elevations in anticipatory reward from food [100]. Rats exposed to intermittent sugar availability show signs of dependence (escalation in bouts of an abnormally large intake of sugar, μ-opiod and dopamine receptor changes, and deprivation-induced sugar binges) and somatic, neurochemical, and behavioral signs of opioid withdrawal that are precipitated by administration of naloxone, as well as cross-sensitization with amphetamine [100,101]. Experimentally induced drug cravings among addicted adults activate the right OFC [102,103], paralleling activation in this region caused by exposure to food cues [93], suggesting that disrupted orbitofrontal activity could give rise to overeating.

Self-reported food cravings correlate positively with BMI and objectively measured caloric intake [22,104,105,106]. Obese individuals report stronger craving of high-fat, high-sugar foods than lean individuals [16,107,108]. Obese adults work harder for food and work for more food than lean adults [19,37,109]. Relative to lean children, obese children are more likely to eat in the absence of hunger [110] and work harder for food [111].

Studies have compared the brain activation in response to presentation of food cues among obese verse lean individuals. Karhunen [112] found increased activation in the right parietal and temporal cortices after exposure to food images in obese but not lean women and that this activation correlated positively with hunger ratings. Rothemund [113] found greater dorsal striatum responses to pictures of high-calorie foods in obese verse lean adults and that BMI correlated positively with response in insula, claustrum, cingulate, postcentral gyrus (somatosensory cortex) and lateral OFC. Stoeckel [114] found greater activation in the medial and lateral OFC, amygdala, ventral striatum, medial prefrontal cortex, insula, anterior cingulate cortex, ventral pallidum, caudate, and hippocampus in response to pictures of high-calorie versus low-calorie foods for obese relative to lean individuals. Stice, Spoor, and Marti [115] found that BMI correlated positively with activation in the putamen (Fig 2) in response to pictures of appetizing food versus unappetizing food and activation in the lateral OFC (Fig 3) and frontal operculum in response to pictures of appetizing food versus glasses of water.

Although the above neuroimaging studies have advanced our understanding of the responsivity of certain brain regions to food images, it is not clear whether these studies capture anticipation of food intake, since they did not involve consumption of the food stimuli during scanning. To our knowledge, only one imaging study has compared obese to lean individuals using a paradigm in which anticipated receipt of food was investigated. We found that obese adolescents showed greater activation of Rolandic, temporal, frontal and parietal opercular regions in response to anticipation of food consumption relative to lean adolescents [49].

In sum, self-report, behavioral, and brain imaging data suggest that obese individuals show greater anticipated food reward than lean individuals. Thus, obesity may arise as a consequence of a hyper-responsiveness in the anticipatory “wanting” system. We believe the field would

benefit from more imaging studies that directly test whether obese individuals show evidence of greater anticipatory food reward in response to presentation of actual food as opposed to foods that are not obtainable. Importantly, no imaging studies to date have tested whether elevations in anticipatory food reward increase risk for unhealthy weight gain and obesity onset, making this a key priority for future research. It will also be important to test whether elevated intake of high-fat and high-sugar foods contributes to elevated anticipatory food reward.

Moderators of Reward Sensitivity

Two lines of evidence suggest that it is important to examine moderators that interact with abnormalities in food reward to increase risk for obesity. Data indicates that food, psychoactive substance use, and monetary reward activate similar brain regions [23,76,77,86]. Additionally, abnormalities in reward circuitry are associated with obesity, substance abuse, and gambling [9,116]. Indeed, there is mounting evidence of a relation between food and drug reinforcement. Food deprivation increases the reinforcement value of food and psychoactive drugs [117, 118], an effect that is at least partially mediated through changes in dopamine signal [119]. Elevated sucrose preference in animals is associated with greater self-administration of cocaine [120] and sucrose intake reduces cocaine's reinforcing value [121]. Neuroimaging data also suggest similarities in the dopamine profiles of drug abusers and obese individuals [39,122].

Although there are numerous factors that may moderate the relation between abnormalities in food reward and obesity, three in particular seem theoretically reasonable: (1) the presence of genotypes associated with reduced dopamine signaling in reward circuitry (DRD2, DRD4, DAT, COMT), (2) trait impulsivity, which theoretically increases risk for responding to a variety of appetitive stimuli, and (3) an unhealthy food environment.

Genotypes that impact dopamine signaling

Given that dopamine plays a key role in the reward circuitry and is involved in food reward [25,123,124], it follows that genetic polymorphisms that affect the availability of dopamine and functioning of dopamine receptors could moderate the effects of abnormalities in food reward on risk for overeating. Several genes influence dopamine functioning, including those that affect dopamine receptors, transport, and breakdown.

To date, the strongest empirical support has emerged for the *TaqIA* polymorphism of the DRD2 gene. The *TaqIA* polymorphism (rs1800497) has three allelic variants: A1/A1, A1/A2, & A2/A2. *TaqIA* was originally thought to be located in the 3' –untranslated region of DRD2, but it actually resides in the neighboring ANKK1 gene [125]. Estimates suggest that individuals with genotypes containing one or two copies of the A1 allele have 30–40% fewer striatal D2 receptors and compromised brain dopamine signaling than those without an A1 allele [126, 127,128]. Those with the A1 allele have reduced resting glucose utilization in striatal regions (putamen and nucleus accumbens), prefrontal, and insula [70] - regions implicated in food reward. Theoretically, the A1 allele is associated with hypofunctioning of the meso-limbic regions, prefrontal cortex, hypothalamus, and amygdala [9]. Low D2 receptor density associated with the A1 allele putatively makes individuals less sensitive to the activation of dopamine-based reward circuitry, rendering them more likely to overeat, use psychoactive substances, or engage in other activities like gambling to overcome this dopamine deficit [57]. In genetically homogeneous and heterogeneous samples, the A1 allele is associated with elevated obesity [129,130,131,132,133,134,135]. Perhaps because of conditioning that occurs during overeating bouts, individuals with the A1 allele report greater food craving, work for more food in operant tasks, and consume more food *ad lib* than those without this allele [37, 116].

Importantly, the relation between abnormalities in food reinforcement and objectively measured food intake is moderated by the A1 allele. Epstein [136] found an interaction between A1 allele and anticipatory food reward among adults, such that the greatest food intake occurred for those who reported elevated reinforcement from food and had the A1 allele. Likewise, Epstein [37] found a significant interaction between the A1 allele and anticipatory food reward among adults, such that the greatest food intake occurred among those who worked the hardest to earn snacks and had the A1 allele. As noted, Stice [49] found that the relation between a blunted dorsal striatal response to food receipt predicted increased risk for future weight gain over a 1-year follow-up for individuals with an A1 allele.

The 7-repeat or longer allele of the DRD4 (DRD4-L) gene has been linked to reduced D4 receptor signaling in an in vitro study [137], to poorer response to methylphenidate in attention deficit/hyperkinetic disorders [138,139], and to less dopamine release in the ventral striatum after nicotine use [140], suggesting it may be related to reward sensitivity. The DRD4 is a postsynaptic receptor that is principally inhibitory of the second messenger adenylate cyclase. Thus, it has been conjectured that those with the DRD4-L allele may show greater impulsivity [138]. D4 receptors are predominantly localized in areas that are innervated by mesocortical projections from the ventral tegmental area, including the prefrontal cortex, cingulate gyrus, and insula [141]. Humans with versus without the DRD4-L allele have shown higher maximum lifetime BMI in samples at risk for obesity, including individuals with Seasonal Affective Disorder who report overeating [142], individuals with bulimia nervosa [143], and African-American adolescents [144], but this relation did not emerge in two samples of adolescents [145,146]. It may be difficult to detect genetic effects in a sample of individuals who have not yet passed through the period of greatest risk for obesity onset. Adults with versus without the DRD4-L allele have shown increased food cravings in response to food cues [147], increased smoking cravings and activation of the superior frontal gyrus and insula in response to smoking cues [148,149], increased alcohol cravings in response to tasting alcohol [150], and increased heroine craving in response to heroine cues [151].

Phasically released dopamine is normally eliminated by rapid reuptake through the dopamine transporter (DAT), which is abundant in the striatum [152]. DAT regulates synaptic dopamine concentration by reuptake of the neurotransmitter into presynaptic terminals. Lower DAT expression, which is associated with the 10 repeat allele (DAT-L), may reduce synaptic clearance and therefore produce higher basal dopamine levels, but blunted phasic dopamine release [140]. Pecina [153] found that disruption of the DAT gene produced increased synaptic dopamine along with an elevated energy intake and preference for palatable foods in mice. A high-fat diet significantly decreased DAT density in the dorsal and ventral parts of the caudal caudate putamen compared to a low-fat diet in mice [154]. Lower striatal DAT availability has been associated with elevated BMI in humans [155]. DAT-L has been associated with obesity in African American smokers, but not in other ethnic groups [156]. Adults with versus without the DAT-L allele showed blunted phasic release of dopamine in response to cigarette smoking [140].

Catechol-o-methyltransferase (COMT) regulates extrasynaptical dopamine breakdown, particularly in the prefrontal cortex, where COMT is more abundant than in the striatum [157]. However, COMT also has a small local effect in the striatum [158] and influences dopamine levels in the striatum via the glutamatergic efferents from the prefrontal cortex to the striatum [159]. A single nucleotide exchange in the COMT gene, which causes a valine to methionine (Val/Met-158) substitution produces a 4-fold reduction in COMT activity in Met relative to Val homozygotes, putatively causing the Met homozygotes to have increased tonic dopamine levels in the prefrontal cortex and striatum and less phasic release of dopamine [140,159]. People with versus without the Met allele show elevated general reward sensitivity as indexed by BOLD responses during reward anticipation or reward selection [160,161] and

substance use [162]. Wang [154] found that individuals with the Met allele versus without were more likely to show at least a 30% increase in BMI from age 20 to age 50 (based on retrospective reports).

Trait impulsivity

It has been theorized that impulsive individuals are more sensitive to cues for reward and more vulnerable to the omnipresent temptation of palatable foods in our obesogenic environment [164,165] leading to the hypothesis that the greatest weight gain will occur for youth showing food reward abnormalities and trait impulsivity. Self-reported impulsivity correlates positively with obesity status [166,167,168] objectively measured caloric intake [169] and negatively with weight loss during obesity treatment [169,170,171]. Obese relative to lean individuals show more difficulties with response inhibition on behavioral go-no-go and stop-signal tasks and show more sensitivity to reward in a gambling task [172,173]. Overweight versus lean children consume more calories after exposure to food cues, such as smelling and tasting a palatable food [174], suggesting that the former are more likely to give in to cravings resulting from food cues. Obese relative to lean individuals have shown a preference for high immediate gain, but larger future losses on behavioral measures in some studies [5,175], but not others [173,176].

Affect regulation expectancies

We also hypothesize that among individuals with abnormalities in food reward, those who believe that eating reduces negative affect and enhances positive affect would be more likely to overeat and show excessive weight gain relative to those not holding these beliefs. Indeed, different affect-regulation expectancies may be a key moderator that determines whether individuals with abnormalities in general reward sensitivity show onset of obesity, versus substance abuse; we posit that those who believe eating improves affect are more likely to go the former route, whereas those who believe that substance use improves affect may be more likely to go the latter route. Corr [177] has likewise posited that the relation between reward sensitivity and response to that reward is moderated by individual differences in affect-regulation expectancies. In support, self-reported reward sensitivity was only related to reward responsivity on a behavioral task for participants who expected the task to be reinforcing [178]. More generally, individuals who believe that eating reduces negative affect and improves positive affect are more likely to show increases in binge eating over a 2-year follow-up than those not holding this belief [179]. We found that among individuals who binge eat, those who believe that eating reduces negative affect and improves positive affect are more likely to show persistence of binge eating over a 1-year follow-up relative to those not holding this belief [180]. Further, individuals who believe that smoking and alcohol use improves affect are more likely to show increases in their smoking and alcohol use relative to those not holding these affect-regulation expectances [181,182].

Food Environment

Researchers have argued that the prevalence of high-fat and high-sugar foods in the home, schools, grocery stores, and restaurants increases risk for obesity [183,184,185]. Theoretically, cues for unhealthy foods (sight of the packaging, the smell of French fries) increase the likelihood of intake of these foods, which contributes to unhealthy weight gain [186]. Individuals who live in homes with many high-fat and high-sugar foods eat more of these unhealthy foods, whereas those who live in homes with fruits and vegetables eat more of these healthy foods [187,188,189]. Most foods sold in vending machines and *a la carte* at schools are high in fat and sugar [185,190]. Students at schools with vending machines and *a la carte* shops consume more fat and less fruits and vegetables than students in other schools [190]. Over 35% of adolescents eat fast food daily and those who frequent these restaurants

consume more calories and fat than those who do not [191]. Fast food restaurants are often closely located to schools [192]. At the regional level, fast food restaurant density is associated with obesity and obesity-related morbidity [193,194,195], though null findings have also been reported [196,197]. Thus, we hypothesize that the relation of abnormalities in food reward to risk for future weight gain will be stronger for participants in an unhealthy food environment.

Conclusions and Directions for Future Research

In this report we reviewed recent findings from studies that have investigated whether abnormalities in reward from food intake and anticipated food intake correlate with concurrent BMI and future increases in BMI. Overall, the literature suggests that obese versus lean individuals anticipate greater reward from food intake; relatively consistent findings have emerged from studies using brain imaging, self-report and behavioral measures to assess anticipatory food reward. Further, studies using self-report and behavioral measures found that obese relative to lean individuals report greater reward from food intake and that preferences for high-fat and high-sugar foods predict elevated weight gain and increased risk for obesity. Brain imaging studies have likewise found that obese compared to lean individuals show greater activation in the gustatory cortex and somatosensory cortex in response to food receipt, which may imply that consuming food is more pleasurable from a sensory perspective. However, several imaging studies also found that obese showed less activation in the dorsal striatum in response to food intake relative to lean individuals, suggesting blunted activation of reward circuitry. Thus, as noted, extant data do not lend clear support to a simple hyper-responsivity or a simple hypo-responsivity model of obesity.

Given this set of affairs, and the evidence from animal studies suggesting that intake of high-fat and high-sugar foods results in down-regulation of D2 receptors, we propose a provisional working conceptual model (Fig 4) in which we posit that people at risk for obesity initially show a hyperfunctioning in the gustatory cortex as well as in the somatosensory cortex that makes consuming food more pleasurable from a sensory perspective, which may lead to greater anticipatory reward from food and increased vulnerability to overeating, resulting in consequent unhealthy weight gain. We hypothesize that this overeating may lead to receptor down-regulation in the striatum secondary to excessive intake of overly rich foods, which may increase the likelihood of further overeating and continued weigh gain. Yet, it is important to note that obese compared to lean showed elevated activation in the dorsal striatum in response to anticipated food intake, suggesting a differential impact on anticipatory and consummatory food reward.

A priority for future research will be to test whether abnormalities in brain reward circuitry increase risk for unhealthy weight gain and onset of obesity. Only one prospective study thus far has tested whether abnormalities in brain regions implicated in anticipatory and consummatory food reward increase risk for future weight gain. Specifically, future studies should examine whether somatosensory and striatum disturbances are primary or secondary to a chronic intake of a high-fat, high-sugar diet. It will be important to test key assumptions regarding the interpretation of these findings, such as whether reduced sensitivity of the somatosensory and gustatory regions translates into reduced subjective pleasure during food intake. Future research should also strive to resolve the apparently inconsistent findings suggesting that obese individuals show hyper-responsivity of some brain regions to food intake, but hypo-responsivity of other brain regions, relative to lean individuals. There is a particular need to integrate measurement of dopamine functioning with functional MRI measures of striatal and cortical responses to food. The literature review suggests that dopamine functioning is linked to differences in food reward sensitivity. However, because existing studies in humans have either used functional MRI measures of responses to food, or PET measures of DA binding, but have never measured both in the same participants, it is unclear to what extent

food reward sensitivity is dependent on DA mechanisms and whether this explains the differential responsivity in obese versus lean individuals. Thus, studies taking a multimodal imaging approach utilizing both PET and functional MRI would contribute to an improved understanding of the etiologic processes that give rise to obesity. Finally, recent data from brain imaging studies have allowed us to begin exploring how these abnormalities in food reward may interact with certain genetic and environmental factors, such as genes related to reduced dopamine signaling, trait impulsivity, affect regulation expectancies, and an unhealthy food environment. Future research should continue to explore factors that moderate the risk conveyed by abnormalities in reward circuitry in response to food receipt and anticipated receipt to increase risk for unhealthy weight gain.

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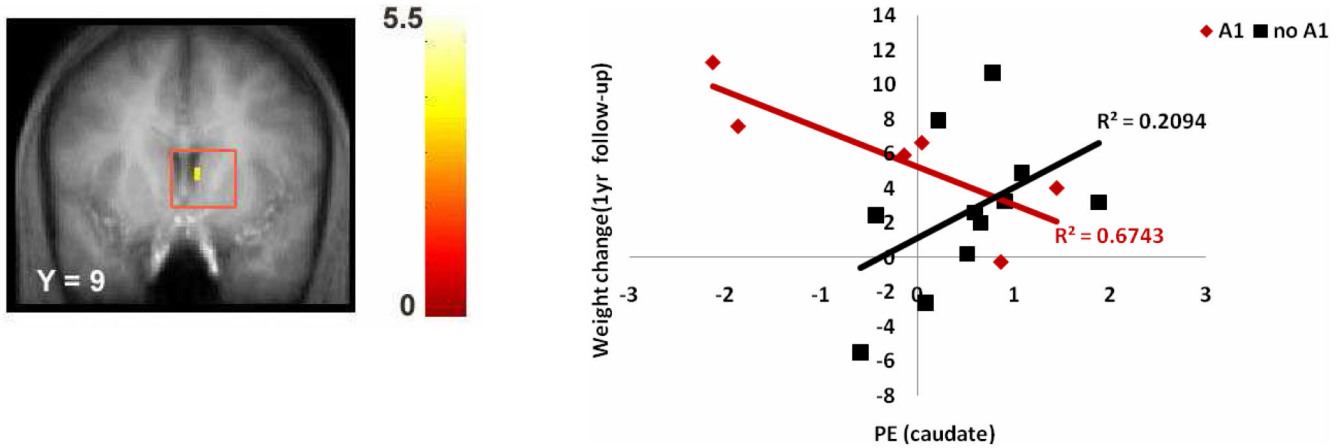
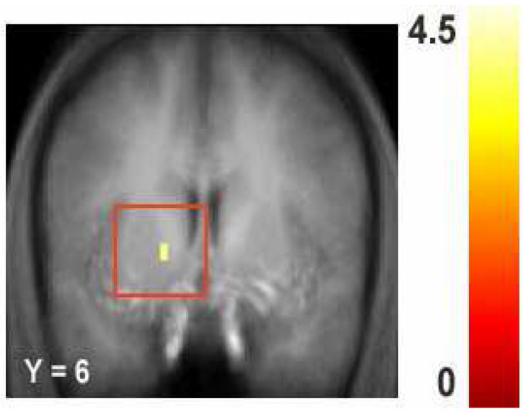


Fig 1.

Coronal section of weaker activation in the caudate (6, 9, 15, z = 2.98, $p_{uncorrected}$ = .002) in response to milkshake receipt versus tasteless solution receipt predicting future weight change for each DRD2 allele type with the graph of parameter estimates (PE) from that region.



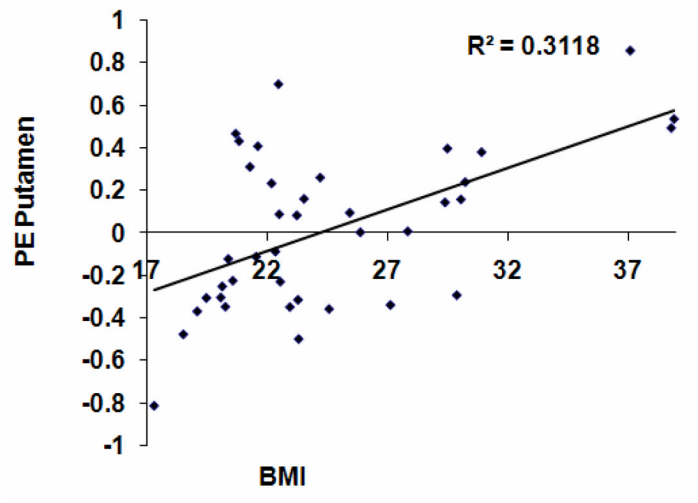


Fig 2.

Coronal section of increased activation in the putamen (-15, 6, 3, z = 3.59, $p_{uncorrected} < .001$) in response to appetizing food – unappetizing food as a function of BMI with the graph of parameter estimates (PE) from that region.

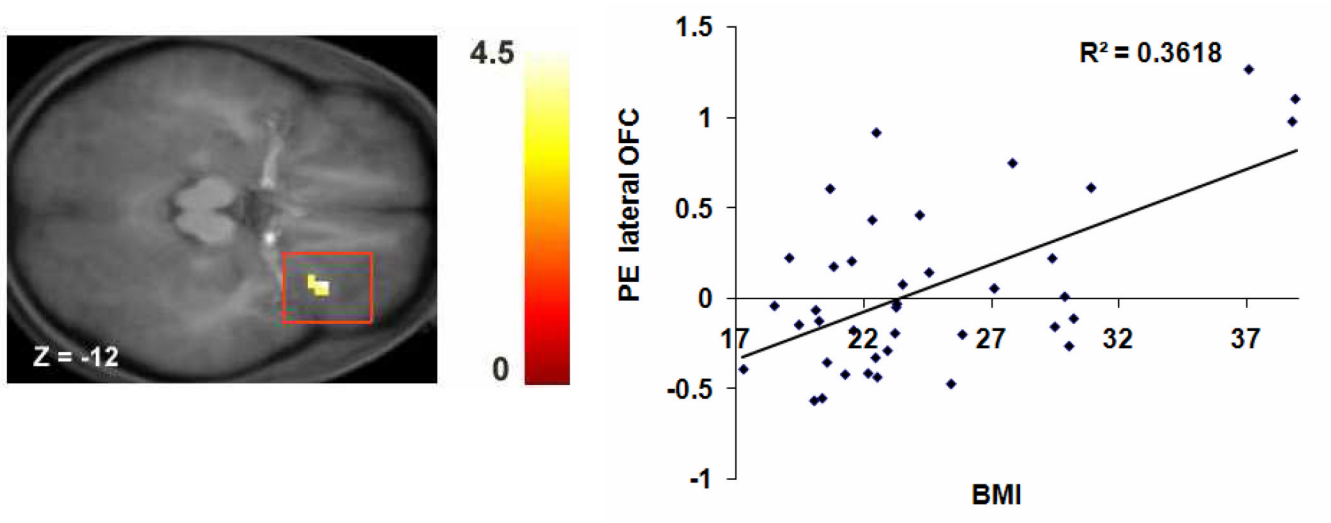


Fig 3.

Axial section of increased activation in the lateral orbitofrontal cortex (OFC) (33, 27, −12, z = 4.01, $p_{uncorrected} < .001$) in response to appetizing food versus water as a function of BMI with the graph of parameter estimates (PE) of that region.

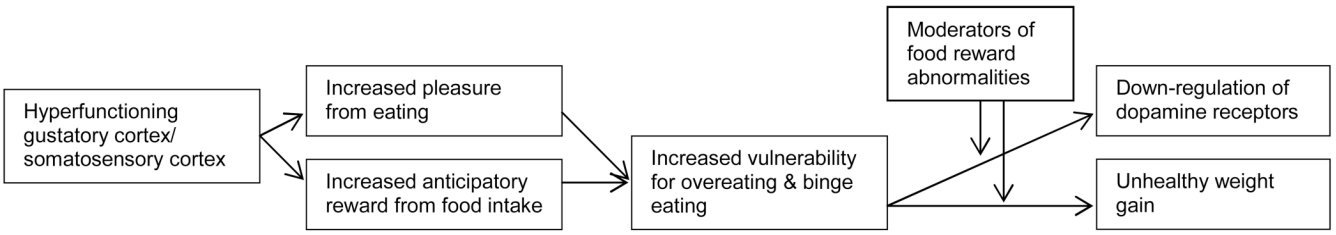


Fig 4.

Working conceptual model presenting the relation between abnormalities in food reward and risk for unhealthy weight gain.