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Variability in Reward Responsivity and Obesity: Evidence from Brain Imaging Studies

Kyle S. Burger and **Eric Stice***
Oregon Research Institute

Abstract

Advances in neuroimaging techniques have provided insight into the role of the brain in the regulation of food intake and weight. Growing evidence demonstrate that energy dense, palatable foods elicit similar responses in reward-related brain regions that mimic those of addictive substances. Currently, various models of obesity's relation to reward from food have been theorized. There is evidence to support a theory of hypo-responsivity of reward regions to food, where individuals consume excess amounts to overcome this reward deficit. There is also data to support a theory of hyper-responsivity of reward regions, where individuals who experience greater reward from food intake are at risk for overeating. However, these seemingly discordant theories are static in nature and do not account for the possible effects of repeated overeating on brain responsivity to food and initial vulnerability factors. Here we review data that support these theories and propose a dynamic vulnerability model of obesity that appears to offer a parsimonious theory that accommodates extant findings.

Keywords

neuroimaging; functional MRI; food reward; obesity; addiction; striatum; dopamine; TaqIA A1 allele

Obesity is associated with increased risk for 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]. In the US 65% of adults are overweight or obese [2]. Unfortunately, virtually all treatments result in only transient weight loss and most prevention programs do not significantly reduce risk for future weight gain [3, 4]. The limited success of treatment and prevention interventions may be due to an incomplete understanding of the processes that increase risk for obesity. Brain imaging techniques, including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), are increasingly being employed to investigate the neural basis of eating behavior, weight regulation and the development of obesity. Results from these neuroimaging studies often point toward variability in reward responsivity to food, frequently dovetailing with traditional addiction literature. Indeed, mounting evidence suggests similarities between subjective reward from food and psychoactive substances. Food deprivation increases the reinforcement value of food and psychoactive substances [5, 6] and produces improved dopamine (DA) receptor functioning [7]. Elevated sucrose preference in animals is associated with greater self-administration of cocaine [8] and sucrose intake reduces cocaine's reinforcing value [9].

Address correspondence: Eric Stice, 1715 Franklin Blvd. Eugene, OR 97401; Phone: 541-484-2123; Fax: 541-484-1108 estice@ori.org.

The parallels food and drug reward are increasingly evident, yet there remain numerous differences. The foremost differences between the two are: 1) physiological need to consume food to sustain life and 2) the low rate at which drug addiction occurs relative the prevalence of obesity. Individuals are born with an innate preference for sweet as a mechanism to maintain adequate energy for growth [10], and develop a preference for fat before the introduction solid foods if not in early childhood [11]. This preference for sweet and fat in combination with the current environment that presents large portions of energy-dense foods [12] creates a scenario primed for overeating and obesity. Yet it is important to note that current drugs of abuse capitalize on reward circuitry that evolved to encourage adequate intake of food for the survival of the species (as well as reproductive success). Despite this knowledge, the neural basis of reward responsivity to food and its relation to overconsumption and excess weight remains largely unclear. The purpose of this review is to examine current models of reward responsivity contributing to overeating and present an integrated reward-based model of obesity vulnerability.

Hypo-responsivity of reward circuitry & obesity

Some theorists posit that obese individuals show hypo-responsivity of reward circuitry, which leads them to repeatedly overeat (or use psychoactive drugs) to compensate for this deficiency [13, 14]. Brain imaging studies have identified regions that respond to food receipt and encode the relative perceived pleasantness of foods. Consumption of palatable food activates the midbrain, insula, dorsal striatum, subcallosal cingulate, and prefrontal cortex and these responses decrease as a function of satiety and declines in food pleasantness [15, 16]. Consumption of a pleasant meal is also associated with DA release in the dorsal striatum and the magnitude of release correlates with ratings of meal pleasantness [17].

In line with the reward deficiency model, obese versus lean individuals have lower basal DA levels and D2 receptor availability [18, 19], implying that they show reduced DA receptor binding in reward circuitry. Further, overweight obesity prone rats versus non-obesity prone rats show lower basal DA levels and ex vivo DA release in response to electrical stimulation in nucleus accumbens, dorsal striatum, and medial prefrontal cortex tissue [20]. However, Yang and Meguid reported that obese versus lean rats show more phasic release of DA during feeding [21]. Additionally, in three separate samples, obese versus lean adolescents show less activation in the dorsal striatum in response to consumption of chocolate milkshake (vs tasteless solution) [22, 23].

Findings from the neuroimaging literature also point to an interaction between hypo-responsivity to reward from food and the TaqIA polymorphism (rs1800497; GenBank accession number NP848605.1). Critically, humans who have a TaqIA A1 allele exhibit less striatal activation in response to food intake and show elevated future weight gain (Fig 1; [22]). The TaqIA A1 is also associated with lower D2 striatal receptor availability and reduced striatal resting metabolism [24, 25]. Additionally, those with the TaqIA A1 allele have significantly less gray matter volume in the dopaminergic midbrain than those with the A2 allele [26]. While these are results from studies with relatively small sample sizes that are predominately Caucasian, they echo evidence that substance abuse is associated with low D2 receptor density and blunted sensitivity of reward circuitry [27].

Although these findings suggest that hypo-responsive DA-reward circuitry increases risk for future weight gain, it is possible that consumption of a high-sugar, high-fat foods leads to down-regulation of D2 receptors [28], paralleling neural response to chronic use of psychoactive drugs [29]. Animal studies suggest that repeated intake of sweet and fatty foods results in down-regulation of post-synaptic D2 receptors, increased D1 receptor

binding, decreased D2 sensitivity, and reduced reward sensitivity [30–33]. Given that most participants were initially overweight in our prospective study showing differential patterns of caudate activation associated with weight gain by A1 allele status [22], it is possible that a history of overeating contributed to the observed predictive effect. Thus, we tested whether overeating was associated with an attenuated striatal response to palatable food in humans; we found that women who gained weight over a 6-month period (n=8) showed a reduced striatal response to chocolate milkshake relative to baseline and women who did not gain weight (n=12; Fig 2; [34]). This finding dovetails with evidence that weight loss increases D2 receptor availability [35], is associated with increased striatal responsivity to food pictures [36], and suggests that reduced responsivity of DA-based reward circuitry may be a consequence of overeating, rather than an initial vulnerability factor. Unfortunately in this case, the sample was not large enough to reliably investigate the influence of TaqIA A1 allele status.

Hyper-responsivity of reward circuitry & obesity

Other theorists posit that individuals who experience greater reward from food intake are at risk for overeating [23, 28, 37]. This is akin to the reinforcement sensitivity model of substance abuse, which posits that certain people show greater reactivity of brain reward systems to reinforcing drugs [37]. In line with this thesis, in response to pictures of palatable foods, obese versus lean humans show greater activation in the striatum, insula, orbitofrontal cortex (OFC), and amygdala [38–40], which are regions that encode the reward value of stimuli [41–43]. In response to anticipated receipt of palatable foods, obese versus lean humans also show greater activation in the primary taste cortex (anterior insula, frontal operculum), which encodes tastes such as sweetness, and in oral somatosensory regions (Rolandic operculum, operculum) [23] which encodes properties such as viscosity and fat texture that signal the caloric density of food [44].

The overall pattern of findings suggest a dissociation between reward from food receipt and the incentive salience of food cues, wherein obese humans show less activation of reward regions to food receipt, but greater activation in regions that encode the reward value of food cues. Incentive salience theory posits that reward from receipt and anticipation operate in tandem with the development of the reinforcing value of food, but after repeated presentations of food, hedonics decrease, while anticipatory reward increases [45]. This is supported by animal literature where, after repeated exposure to sugar, DA release was deceased during sugar receipt [46]. Additionally, hyper-responsivity to anticipation could be a function of altered reward and behavioral control brain networks, as chronic heroin users show greater resting-state functional connectivity between the nucleus accumbens and the anterior cingulate (ACC) and the OFC and decreased connectivity between the prefrontal cortex and OFC and ACC relative to matched controls [47]. Importantly, a prospective study revealed that individuals who showed greater activation in the OFC in response to cues for appetizing versus unappetizing food images showed elevated future weight gain (Fig 3; [48]). Mirroring the moderating effects of the TaqIA A1 allele noted above, blunted response of the dorsal striatum and frontal operculum to food images predicted future increases in BMI for those with an A1 allele, but elevated activation in these regions predicted weight gain for those without the A1 allele (Fig 4; [40]). Findings suggest that individuals who show hyper-responsivity of regions that encode the incentive salience of food cues are at increased risk for future weight gain and that these predictive effects are moderated by A1 allele status.

However, it is not clear whether hyper-responsivity of reward regions to food receipt or anticipated receipt represent initial vulnerability factors for overeating. Animal experiments indicate that, after conditioning, the reward value of food shifts from food intake and to

anticipated food. For example, naïve monkeys showed activation of mesotelencephalic DA neurons only in response to a rewarding food taste; however, after conditioning, activation began to precede reward delivery and eventually maximal activity was elicited by the conditioned stimuli that predicted food reward rather than by actual food receipt [49]. Additionally, Kiyatkin and Gratton (1994) found that the greatest dopaminergic activation occurred in an anticipatory fashion as rats approached and pressed the bar that produced food reward, with activation decreasing as the rat received and ate the food. Blackburn et al. (1989) found that DA 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. There is also evidence that a history of elevated sugar intake may contribute to excess elevations in anticipatory reward from food [50]. Rats exposed to intermittent sugar availability show signs of dependence (escalation in sugar binging, mu-opioid and DA receptor changes, and deprivation-induced sugar binges) and somatic, neurochemical, and behavioral signs of opioid withdrawal [50]. This withdrawal can be precipitated by naloxone, suggesting that opioids play a major role in sugar dependence [50]. Additionally, a diet of intermittent excessive sugar consumption is associated with cross-sensitization of amphetamine, suggesting an alteration in the DA system [51]. Collectively these data indicate that repeated exposure of a rewarding food (i.e., conditioning of food receipt and its preceding cues) generates in a shift in the reward responsivity, suggesting a more complex model leading to overeating and subsequent obesity.

Dynamic theories of reward circuitry & obesity

Thus, at present it is unclear whether the initial vulnerability for obesity is the hypo-responsivity of the striatum to food receipt or the hyper-responsivity of regions that encode the incentive salience of food cues, given the evidence that overeating may lead to the development of both of these anomalies and the fact that most participants in our prior prospective studies were already overweight at baseline. Extant findings are generally consistent with three theories regarding initial vulnerability and the etiologic process that causes obesity. One theory is that individuals at risk for obesity experience: 1) initial weaker dorsal striatal activation from food intake, leading them to overeat palatable foods to compensate for this reward deficit and also 2) the emergence of hyper-responsivity of regions that encode incentive salience of food cues through conditioning that occurs after repeated overeating episodes (initial hypo-reward model). A second theory is that individuals at risk for obesity show: 1) initial hyper-responsivity of regions that encode the incentive salience of food cues, leading to overeating and 2) a consequent reduction in D2 receptor density in the striatum and blunted DA signaling in response to food intake (hyper-incentive sensitization model). A third theory is that individuals at risk for obesity experience: 1) initial hyper-reward responsivity from food intake, leading to overeating which 2) reduces striatal D2 receptor density and DA signaling in response to food intake, as well as the emergence of 3) hyper-responsivity of regions that encode the incentive salience of food cues through conditioning during repeated bouts of overeating, both of which may drive further overeating in a feed-forward fashion (dynamic vulnerability model). This latter model accords with the thesis that hyper-responsivity of reward circuitry increases risk for overeating [23, 28, 37], though it adds the notion of plasticity in reward circuitry's response to food after overeating occurs.

To evaluate these three models, we tested whether lean adolescents at high versus low risk for obesity – by virtue of dual parental obesity – showed greater or weaker activation of DA-based reward circuitry in response to receipt and anticipated receipt of palatable food (N=60). We also contrasted activation in response to receipt and anticipated receipt of money to determine whether any anomalies in reward-related regions were specific to food

or generalized. High-risk versus low-risk youth showed greater caudate, parietal operculum, and frontal operculum activation in response to food receipt, as well as evidence of greater caudate, putamen, insula, and OFC activation in response to money receipt (Fig 5; [52]). However, high-risk versus low-risk youth did not show a differential response to anticipated food or monetary receipt [52]. Importantly, the enhanced opercular responses, observed selectively to milkshake receipt, correspond to oral somatosensory cortex, which represents the viscosity of oral stimuli [44]. These preliminary findings align with evidence that obese versus lean individuals show elevated responsivity in somatosensory regions in response to anticipated receipt of palatable foods [23] and images of palatable foods [40], greater regional blood flow in somatosensory regions in response to images of palatable foods [53], and greater resting glucose metabolism in the oral somatosensory cortex [54]. Moreover, since oral viscosity is a primary sensory signal of the fat content of foods, these findings also accord with evidence that obese versus lean humans rate high-fat foods as more pleasant and consume more of such foods [55–58], obese prone rats showed greater sensitivity to oral fat [59], and 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 [60–62]. Research also indicates that preferences for high-fat foods predict elevated future weight gain [61, 63–65]. These preliminary data suggest that youth at risk for obesity initially show greater responsivity of reward circuitry, coupled with elevated responsivity of oral somatosensory regions to food, but no differences in anticipation of reward supporting the first stage of the dynamic vulnerability model. Previous prospective data, specifically the inverse relation between weight gain and striatum activity in response to food receipt (Fig 2; [34]) and the positive relation of weight gain and OFC activity in response to palatable food images (Fig 3; [48]) support the later stages of the dynamic vulnerability model. However, extent studies have not provide a test of all aspects of the dynamic vulnerability model, which would require repeated fMRI scans during a period of time in which some subjects develop obesity and others do not.

Additionally, we compared genetic data of the youth at high-risk versus low-risk for obesity. Although the prevalence of the TaqIA A1 allele was three times greater in youth at high-risk versus low-risk for obesity (35% vs. 12%; $t(58) = 2.00$, $p = .05$), this genotype was not significantly related to striatal response to food receipt or anticipated receipt. This is in contrast to results from overweight samples, wherein A1 allele status correlated with reduced response to palatable food intake in DA source and target regions [22, 66]. This hints at a possible gene-environment interaction in which A1 allele status only increases risk for a blunted striatal response if paired with overeating or elevated adiposity. This possibility is in line with the thesis of plasticity of striatal response to food intake secondary to overeating. Further, the TaqIA polymorphism is located on the novel ANKK1 (ankyrin repeat and protein kinase domain-containing progestin 1) just downstream from the DRD2 receptor [67] and is thought to regulate this receptor via inflammatory processes [68]. Given that obesity is associated with chronic low-grade inflammation, an intriguing, though speculative hypothesis is that overeating or elevated adiposity is associated with an inflammatory process that reduces striatal D2 receptor expression. This notion is supported by reports that weight-associated inflammation is related to the reduction of the microstructural integrity of brain regions involved with food reward and eating behavior [69]. This working hypothesis aligns with evidence that blunted dorsal striatal response to food and blunted dorsal striatal, OFC, and frontal operculum response to food images only increases risk for future weight gain among individuals with the A1 allele [22, 40, 66]. This pattern of findings suggests that TaqIA A1 allele status may amplify the predictive effects of the vulnerability factors to be examined herein.

Conclusion

Collectively, extant findings suggest the possibility of a dynamic vulnerability model for obesity that may evolve and change over time in response to overeating and/or fat accumulation (Fig 6). We submit that individuals at risk for obesity initially show hyper-responsivity of the striatum to general reward and somatosensory regions in response to palatable, energy dense foods, which increases risk for overeating. We posit that the oral somatosensory responses reflect altered sensitivity for fat and/or enhanced preference for high-fat foods. We further submit that overeating, especially in individuals with an A1 allele polymorphism, may in turn result in a down-regulation of DA-based reward regions, producing a blunted striatal response to food intake, which may lead people to overeat in an effort to achieve the same subjective reward from palatable food they initially felt in a feed forward manner. The overeating may also result in greater responsivity of regions that encode the incentive salience of food cues, which might be moderated by TaqIA A1 allele status, making people more vulnerable to food cues in our obesogenic environment, which also may increase risk for escalation of overeating in a feed forward fashion. Although this working dynamic vulnerability model holds promise, it rests on data from prospective fMRI with relatively small, ethnically similar samples.

An additional construct to this model that has been theorized to interact with reward sensitivity is impulsivity. For example, Dawe and Loxton posit in addition to initial hyper-responsivity of the reward pathways those that exhibit impulsive behaviors are likely to overeat [37]. Research has found that both obesity and eating pathology are associated with elevated impulsivity. Both self-reported and laboratory measures of impulsivity correlate positively with caloric intake [70, 71] and body mass index [72–74]. Despite these observed relations, few data are available to elucidate the possible interaction of impulsivity and reward responsivity to food on a neural level, specifically whether impulsive behavior is predisposing or consequential factor of overeating, making this an important priority for future research. It is reasonable to hypothesize that impulsivity is an initial vulnerability to overeating that parallels initial hyper-responsivity to food receipt. However, it is also reasonable to suggest that impulsivity develops through conditioning in a similar matter to the regions that encode the incentive salience of food cues.

Currently studies have investigated individual components of these models with limited reach to capture a more complete picture. It is a possibility that these theories each contribute to overeating and the development of obesity and are more prevalent in certain specific populations (e.g., sex, ethnicity, additional genetic polymorphisms) or specific to components of food (e.g., fat, sugar, caffeine). Thus, it will be important for future repeated-measures brain imaging studies to use both fMRI and PET techniques designed to capture the vulnerability factors that initially give rise to overeating among lean youth at high versus low risk for future weight gain and the changes in neural responsivity that appear to emerge to sustain overeating.

ABBREVATIONS

fMRI	Functional neuroimaging
PET	Positron emission tomography
DA	Dopamine
OFC	Orbitofrontal cortex
ACC	Anterior cingulate cortex

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Key Learning Objectives

- Evaluate current theories of obesity stemming from variability in reward-related brain responsivity to food.
- Identify a dynamic theory of brain responsivity and obesity.

Future Research Questions

- How does brain responsivity to food cues and consumption change as a result of overeating?
- Are the changes in food-related reward processing a result of repeated consumption of rewarding foods or a function physiological change (e.g., excess fat mass; regional changes in brain volumes)?
- Are initial vulnerability factors of obesity evident on a neural level? If so, can they be addressed to prevent excess weight gain?

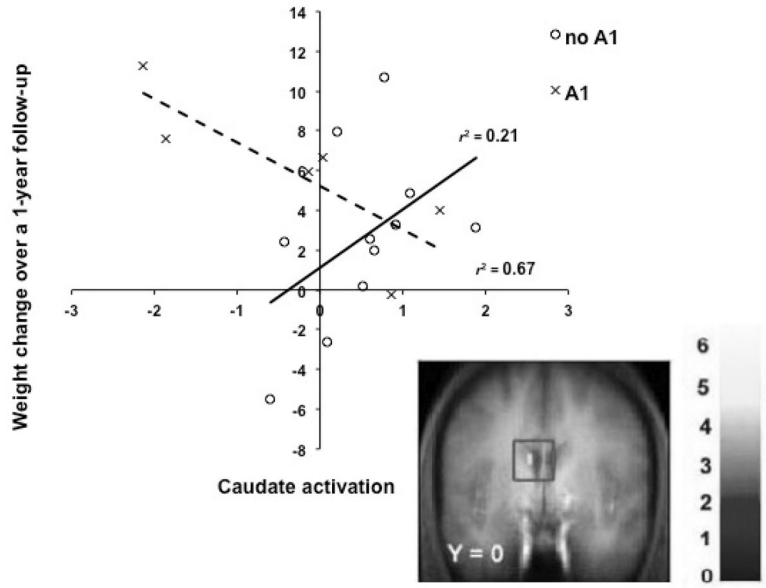

Figure 1.

Differential activation in the caudate in response to milkshake receipt (contrasted with tasteless receipt) across weight change over one year by TaqIA A1 status. Those with the A1 allele (dashed line) show decreases in activation as weight increases, whereas those without the A1 allele (solid line) show increases in activation as weight increases [22].

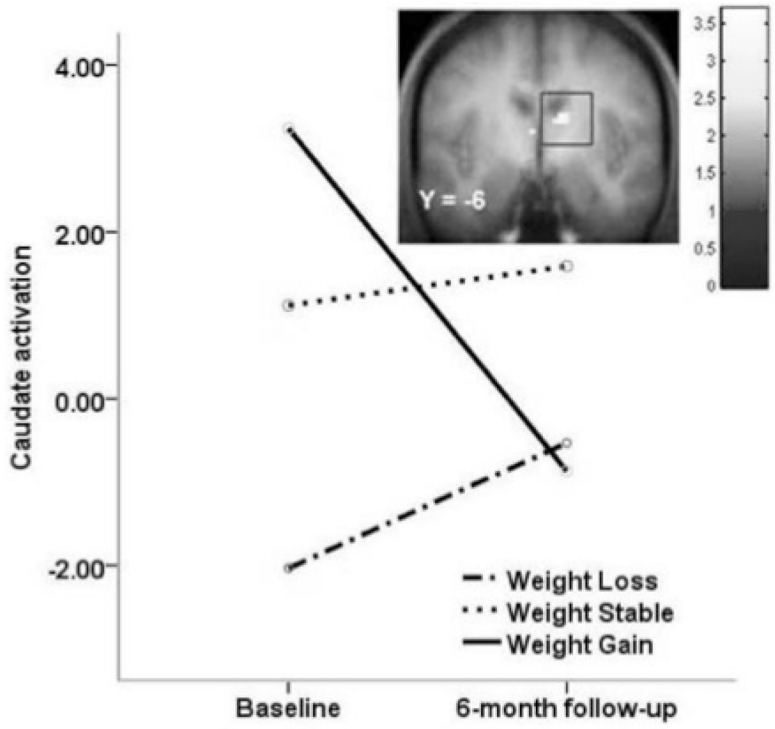

Figure 2.
Decreased activation in the caudate in response to milkshake receipt (contrasted with tasteless receipt) by weight change group over a 6-month period. Those that gained weight (solid line) showed decreases in activation, whereas those that lost weight (dashed line) or were weight stable (dotted line) showed slight increases in activation in this region [34].

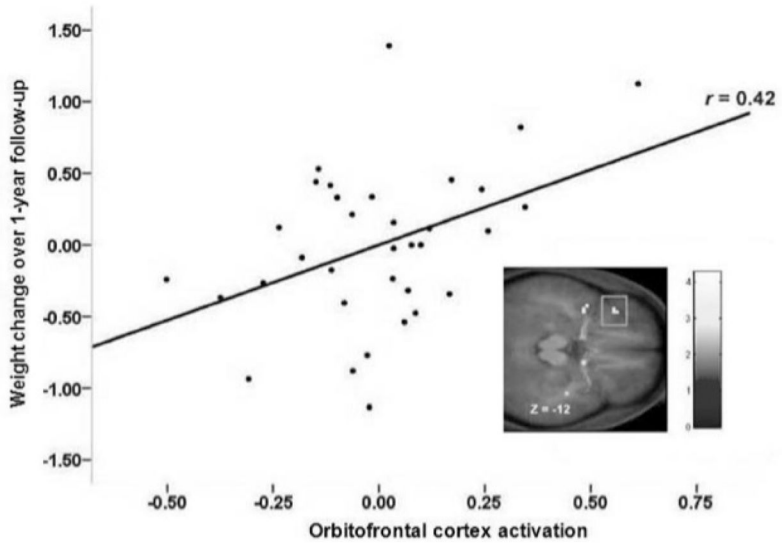

Figure 3.
Activation in the orbitofrontal cortex in response to initial orientation to appetizing food images (contrasted with pictures of glasses of water) related to weight change over a one-year period [48].

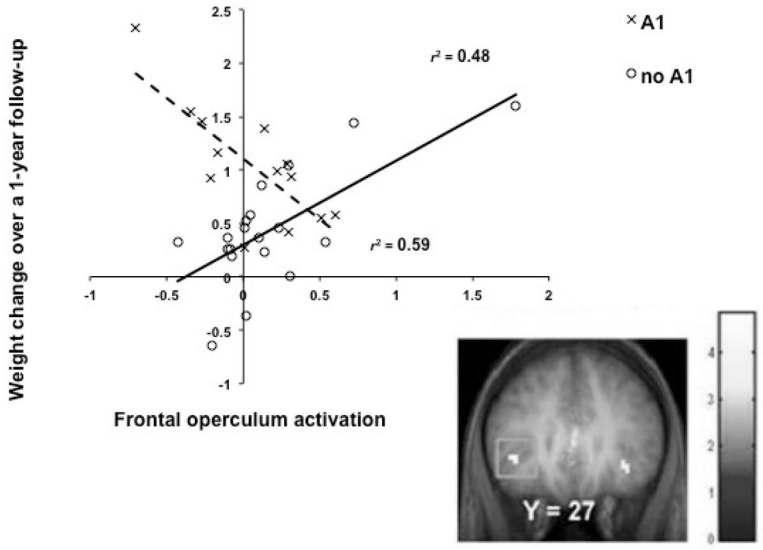

Figure 4.

Differential activation in the frontal operculum in response to appetizing food pictures (contrasted with pictures of glasses of water) across weight change over one year by TaqIA A1 status. Those with the A1 allele (dashed line) show increases in activation as weight decreases, whereas those without the A1 allele (solid line) show increases in activation as weight increases [40].

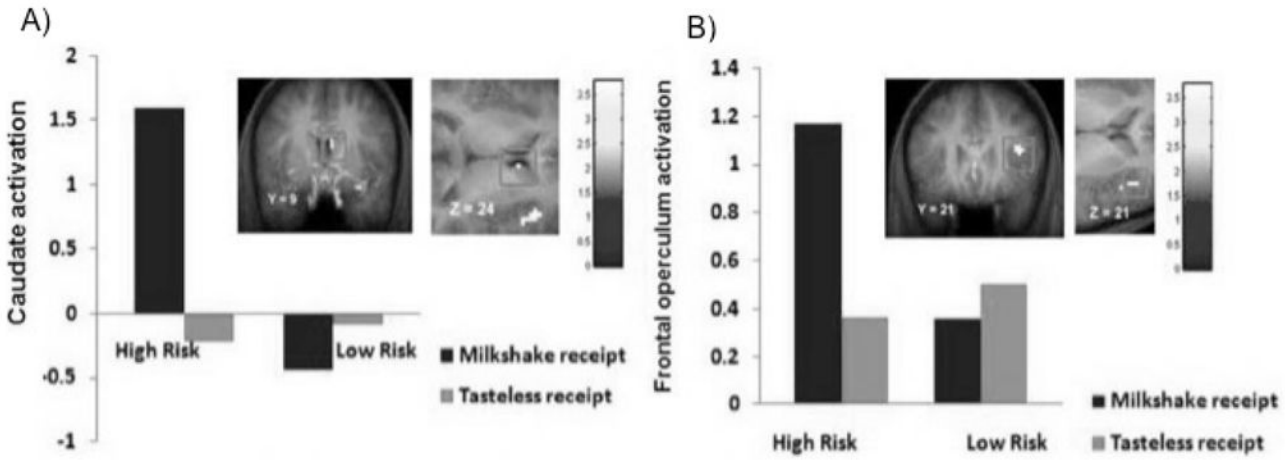

Figure 5.

Greater activation in the A) caudate and B) frontal operculum in adolescents at a high risk for obesity vs. adolescents at a low risk for obesity in response to milkshake receipt (contrasted with tasteless receipt). Despite no difference in current BMI, adolescents at high risk for obesity show greater activation in these reward and gustatory related regions to a palatable food [52].

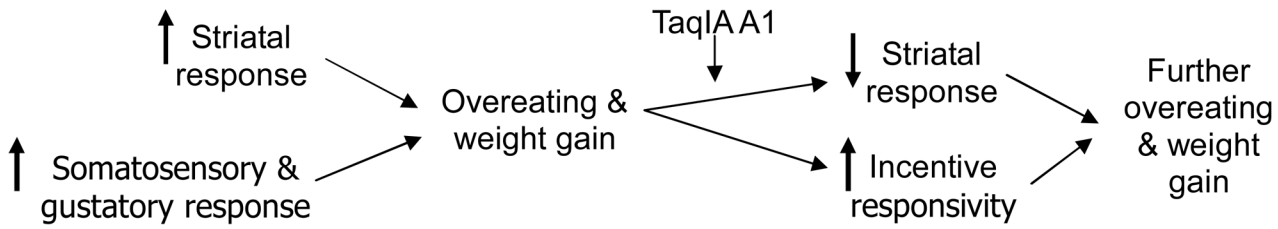

Figure 6.
Dynamic vulnerability model of obesity