HHS Public Access

Author manuscript

Clin Psychol Rev. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

Clin Psychol Rev. 2019 March ; 68: 38–53. doi:10.1016/j.cpr.2018.12.002.

Neural Vulnerability Factors for Obesity

Eric Stice and
Oregon Research Institute

Kyle Burger
University of North Carolina

Abstract

Multiple theories identify neural vulnerability factors that may increase risk for overeating and weight gain. Early cross-sectional neuroimaging studies were unable to determine whether aberrant neural responsivity was a risk factor for or a consequence of overeating. More recent obesity risk, prospective, repeated-measures, and experimental neuroimaging studies with humans have advanced knowledge of etiologic processes and neural plasticity resulting from overeating. Herein, we review evidence from these more rigorous human neuroimaging studies, in conjunction with behavioral measures reflecting neural function, as well as experiments with animals that investigated neural vulnerability theories for overeating. Findings provide support for the reward surfeit theory that posits that individuals at risk for obesity initially show hyper-responsivity of reward circuitry to high-calorie food tastes, which theoretically drives elevated intake of such foods. However, findings provide little support for the reward deficit theory that postulates that individuals at risk for obesity show an initial hypo-responsivity of reward circuitry that motives overeating. Further, results provide support for the incentive sensitization and dynamic vulnerability theories that propose that overconsumption of high-calorie foods results in *increased* reward and attention region responsivity to cues that are associated with hedonic reward from intake of these high-calorie foods via conditioning, as well as a simultaneous *decrease* in reward region responsivity to high-calorie food tastes. However, there is little evidence that this induced reduction in reward region response to high-calorie food tastes drives an escalation in overeating. Finally, results provide support for the theory that an initial deficit in inhibitory control and a bias for immediate reward contribute to overconsumption of high-calorie foods. Findings imply that interventions that reduce reward and attention region responsivity to food cues and increase inhibitory control should reduce overeating and excessive weight gain, an intervention theory that is receiving support in randomized trials.

Keywords

obesity; fMRI; prospective; reward circuitry; weight gain

Conflicts

Neither author reports any conflict of interest in relation to the literature reviewed in this manuscript.

Obesity results in 2.8 million premature deaths worldwide annually (World Health Organization, 2013). However, treatments rarely result in lasting weight loss and virtually all obesity prevention programs have not reduced future obesity onset (Plotnikoff et al., 2015; Stice, Shaw, & Marti, 2006). An improved understanding of risk factors that predict future weight gain and effective weight regulation should advance knowledge regarding processes that give rise to obesity and guide the design of more effective preventive programs and treatments. Multiple models aim to explain appetitive behavior and weight regulation. These models typically fall into two general categories: 1) homeostatic regulation and, 2) hedonically motivated behavior. Homeostatic regulation is primarily founded in neuroendocrine mechanisms that maintain energy balance, such as the orexigenic hormone ghrelin and the adipokine leptin. Tight regulation of these appetitive hormones served as the basis of the long-standing theory of implicit regulation in the set point theory of obesity (Harris, 1990). Homeostatic regulation of appetite may act on a neural level to influence motivated behavior, including hedonically driving food intake (Burger & Berner, 2014). Theories of hedonically motivated eating behavior center on how aberrant reward processing in the brain contributes to overeating highly palatable energy-dense foods.

Several neural vulnerability factors theoretically increase risk for the excess energy intake that drives excess weight gain. For example, increasing evidence point to an association between elevated weight and altered neural functioning. For example, obese versus healthy weight individuals show decreased functional connectivity within prefrontal networks, reward networks (e.g., insula and caudate), and the salience network (García-García, I. et al., 2013, Geha et al., 2016). Obesity has also been associated with increased connectivity within the attention network (premotor areas, superior parietal lobule, and visual cortex), as well as, stronger hypothalamic-striatal and amygdala-insular connectivity (Lips et al., 2014). Collectively, these cross-sectional data suggest that elevated weight is associated with disruption in the functional integration of brain regions and networks that encode aspects of hedonically motivated behaviors and gustatory and attentional processing while at rest. These data are of importance as they are not in response to food stimuli, but may be priming individuals when food stimuli are present.

Experiments also indicate that high-calorie food intake activates regions implicated in reward processing, including the striatum, midbrain, amygdala, and orbitofrontal cortex (OFC; Kringelbach et al., 2003; Small et al., 2001; Stice, Burger, & Yokum, 2013). High-calorie food intake likewise causes dopamine release in the dorsal striatum, with the amount released correlating with meal pleasantness ratings (Small et al., 2003) and caloric density of the food (Ferreira et al., 2012). Acute intake of glucose also results in a reduction in the binding potential of [^{11}C]raclopride in men, suggesting an increase in dopamine release, though this effect was opposite in women, potentially because of the small sample size (Haltia et al., 2007). Further, peripheral blood glucose concentrations were significantly correlated with cerebrospinal fluid concentrations of the dopamine metabolite, homovanillic acid, suggesting that elevated intake of high-sugar foods may increase dopamine neuraltransmission (Umhau et al., 2003). Rodent studies confirm that the oral sensory properties of high-sugar and high-fat food consumption stimulate brain dopamine release (Hajnal et al., 2004; Liang et al., 2006). Interestingly, even intra-gastric infusion of glucose and fat, bypassing the oral cavity and gustatory stimulation, induces striatal (nucleus

accumbens) dopamine release in rodents compared to isocaloric infusion of amino acids (Ren et al., 2010; Tellez et al., 2013). Given these effects, etiologic theories have often focused on reward circuitry. Further, anticipated high-calorie food intake (O'Doherty, Deichman, Critchley, & Dolan, 2002; Small, Veldhuizen, Felsted, Mak, & McGlone, 2008; Stice, Yokum, Burger, Epstein, & Smolen, 2012) and food images and cues (Frank et al., 2010; Van Meer, van der Laan, Adan, Viergever, & Smeets, 2015) activate regions implicated in incentive valuation, such as the OFC and amygdala, particularly after caloric deprivation (Leidy et al., 2011). These data have also prompted a focus on regions that encode the incentive valuation in etiologic theories for obesity. Figure 1 illustrates the main central nervous system (CNS) and perifrial organs involved in homeostatic and hedonic control over eating behavior.

It is important to note that high-calorie food intake, anticipated intake, and food cues have broad effects, activating regions implicated in visual processing/attention (inferior parietal lobe, posterior cingulate cortex), gustatory processing (insula and overlying operculum), motor response (precentral gyrus, cerebellum), somatosensory processing (postcentral gyrus), and inhibitory behavior (inferior frontal gyrus, ventrolateral prefrontal cortex) (Huerta, Sarkar, Duong, Laird, & Fox, 2014; Stice et al., 2012; Tang et al., 2012; van Meer et al., 2015).

Animal experiments suggest that dopamine signaling plays a larger role in reward learning, particularly the learning of reward-predictive cues, and that opioid peptide signaling plays a larger role in hedonic pleasure from food intake, largely on the basis that the effects of each neurotransmitter can be isolated experimentally (Berridge et al., 2010; Flegel et al., 2011). Consistent with this thesis, acute administration of an opioid antagonist reduced response in the caudate, anterior cingulate cortex, and medial frontal gyrus to the sight and taste of high-calorie food relative to a placebo control condition (Murray et al., 2014). Yet, reward regions (e.g., the midbrain and striatum) contain both dopamine and opioid receptors (Ambrose, Unterwald, & Bockstaele, 2004; Pollard, Llorens-Cortes, & Schwartz, 1977) and μ opioid and dopamine receptor availability in the striatum and ventral tegmental area (VTA) are highly correlated in humans (Tuominen et al., 2015). Further, the two neurotransmitter systems exhibit crosstalk (Tuominen et al., 2015). Mesolimbic dopamine neurons are under tonic gamma aminobutyric acid-ergic (GABA) inhibition that can be lifted through activation of μ opioid receptors on GABAergic terminals in the VTA (Jalabert et al., 2011). Administration of alfentranil, a potent and highly selective μ-opioid receptor agonist, increased PET-assessed dopamine D2 receptor binding potential in the putamen and caudate in humans (Hagelberg et al., 2002). Conversely, amphetamine, which blocks the dopamine transporter that clears dopamine from synapses, thereby increasing dopamine levels, causes the release of opioids in the ventral striatum in humans (Colasanti et al., 2012; Mick et al., 2014). Moreover, blocking striatal opioid receptors attenuates amphetamine-induced locomotion and impulsivity (Gonzalez-Nicolini et al., 2003; Wiskerke et al., 2011), whereas blocking dopamine D2 receptors attenuates the rewarding effects of morphine in opiate-dependent rats (Laviolette, Nader, & Kooy, 2002). This crosstalk is consistent with the notion that dopamine signaling facilitates learning about hedonically rewarding experiences.

Herein, we review the primary theories relating aberrations in responsivity of brain reward and incentive valuation regions, as well as regions that affect activation in these regions (e.g., inhibitory regions), to future weight gain. We briefly discuss behavioral foundations of overeating then move to multiple obesity theories and provide supporting data, ending in the presentation of an integrative model, which attempts to synthesize the initial theories. Data presented focus predominantly on prospective studies and randomized experiments with humans and animals, in addition to high-risk phenotype designs, to elucidate initial vulnerability factors for future weight gain. A summary of key studies and their relation to the various brain-based studies can be seen in Table 1. Lastly, we discuss clinical implications and future directions for research.

Behavioral origins of hedonically motivated food intake

Recent advances in functional neuroimaging in response to food stimuli provide insight to the dynamic processes of hedonically motivated food intake that serve as the basis of many of the conceptual models discussed below. Ultimately, hedonically motivated food intake, prior to weight gain, is a decision-making process influenced by reward learning, regulation of goal-directed behavior, and habit formation. Pavilion conditioning must occur during the early stages of overeating. Specifically, this is referring to the process wherein the reward-related response from tasting an energy-dense, highly palatable food (reward surfeit theory) is repeated until a previously agnostic cue of the food elicits an increased attentional and dopaminergic response as stipulated in the incentive sensitization theory (see below). Subsequently, dopaminergic response during food intake and basal dopamine levels are diminished (reward deficit theory), which may contribute to increase impulsivity. The dynamic process has been repeatedly demonstrated in animal models independent of weight status (Johnson & Kenny, 2010; Phillips, Stuber, Heien, Wightman, & Carelli, 2003; Schultz, 1998). Further, it has emerged in an single scanning session over 16 exposures (Burger & Stice, 2014) and using objective measures of caloric intake over a 2-week period (Burger & Stice, 2013). More importantly, these processes have resulted from daily sugary beverage consumption in a small randomized controlled trial (Burger, 2017). These findings become generalizable to free living food intake given that after a short fast the degree of midbrain and medial OFC response to a palatable food predicted subsequent *ad lib intake* (Nolan-Poupart, et al., 2013).

Incentive Sensitization Theory of Obesity

The incentive sensitization model of obesity posits that repeated intake of high-calorie foods results in an elevated responsivity of regions involved in incentive valuation to cues that are associated with hedonic reward from intake of these foods via conditioning, which prompts craving and overeating when these cues are encountered (Berridge et al., 2010). Animal experiments indicate that firing of striatal and ventral pallidum dopamine neurons initially occurs in response to receipt of a novel high-calorie food, but that after repeated pairings of high-calorie food intake and cues that signal impending receipt of that food, dopamine neurons begin to fire in response to food-predictive cues and no longer fire in response to food receipt (Schultz et al., 1997; Tindell et al., 2004; Tobler et al., 2005). Theorists posit that this shift during cue-reward learning serves to update knowledge regarding the

predictive cues or attribute reward value to the cues themselves, thereby guiding behavior (Balleine et al., 2008; Robinson & Berridge 1993). This theory implies that a period of overeating high-calorie foods may be necessary for the conditioning process that gives rise to hyper-responsivity of reward regions to food cues, suggesting that this might be better viewed as a maintenance model of overeating. Alternatively, it is possible that individual difference factors, such as a genetic propensity for greater dopamine signaling, render some people more likely to attach incentive value to cues for high-calorie foods.

Obese versus lean humans show greater responsivity of brain regions associated with reward and motivation (striatum, amygdala, OFC) to pictures of high-calorie foods versus low-calorie foods and control images in both fasted and fed states (e.g., Bruce et al. 2010; Dimitropoulos, Tkach, Ho, & Kennedy, 2012; Frankort et al., 2012; Holsen et al., 2012; Martin et al., 2010; Stice, Yokum, Bohon, Marti, & Smolen, 2010b). Similarly, humans with versus without a range of various substance use disorders show greater activation of regions implicated in reward and motivation to substance use images (e.g., Due, Huettel, Hall, & Rubin, 2002; Myrick et al., 2004; Tapert et al., 2003). However, these cross-sectional data provide no evidence of temporal precedence, and are therefore of limited inferential value.

There is emerging evidence that visual, olfactory, and auditory cues for high-calorie foods result in increased future choice and *ad lib* intake of those high-calorie foods in humans (Chambaron, Chisin, Chabanet, Issanchou, & Brand, 2015; Coelho, Polivy, Herman, & Pliner, 2009; Gaillet, Sulmont-Rosse, Issanchou, Chabanet, & Chambaron, 2014). Indeed, elevated responsivity in the ventral striatum (Lawrence, Hinton, Parkinson, & Lawrence, 2012) and amygdala (Mehta et al., 2012) during exposure to food images also predicted greater subsequent *ad lib* high-calorie food intake. Likewise, elevated activation in the medial prefrontal cortex (mPFC) to being informed that participants had won food versus money, as well as greater amygdala and dlPFC response to being informed that participants had won food versus money, predicted greater intake of high-calorie foods (Adise et al., 2018). Of note, healthy weight adolescents who were eating beyond objectively measured basal metabolic needs showed greater response during cues predicting impending palatable food receipt in regions that encode visual processing and attention (visual and anterior cingulate cortices), salience (precuneus; Frohlich, 1994), and reward and motivation (striatum), as well as a region in the primary gustatory cortex (frontal operculum; Burger & Stice, 2013), suggesting that overeating, even if it has not yet resulted in excess weight gain, may be accompanied by elevated responsivity of reward, attentional, and gustatory regions to food predictive cues.

Prospective fMRI studies that used moderate-sized samples have found that elevated nucleus accumbens response to palatable food images (Demos et al., 2012), elevated caudate response to palatable food commercials (Yokum, Gearhardt, Harris, Brownell, & Stice, 2014), and elevated orbitofrontal cortex (OFC) response to cues that predict palatable food image presentation (Yokum et al., 2011) predicted future weight gain. However, one study did not find a main effect between elevated responsivity of brain regions implicated in reward to food cues/images and future weight gain (Stice et al., 2010). Obese individuals who evidenced greater reward and attention region response to high-calorie food images showed a poorer response to behavioral weight loss treatment (Murdaugh et al., 2012),

consistent with the notion that hyper-responsivity of these regions maintain overeating. Yet, as the samples from those studies included overweight individuals, it is possible that a history of overeating might have caused the elevated reward region responsivity to palatable food images. One study recruited healthy weight adolescents to test the thesis that youth who show greater reward region response to palatable food tastes and cues that signal impending palatable food tastes are at risk for initial excessive weight gain; elevated OFC response to cues signaling impending milkshake receipt predicted initial excessive body fat gain (Stice, Burger, & Yokum, 2015), an effect that replicated in split halves of the sample, indicating a robust, stable effect. One repeated-measures fMRI study may have captured the emergence of the incentive sensitization process; it found that adolescents who engaged in overeating over a 3-year period showed an increase in reward valuation region response (putamen, mid-insula) to cues for a high-calorie beverage versus a non-caloric beverage compared to adolescents who were weight stable or who lost weight (Stice & Yokum, 2016).

Interestingly, obese versus lean individuals also show attentional bias for high-calorie food images according to the Stroop test (Braet & Crombez, 2003; Nijs et al., 2010a) and eye tracking (Castellanos et al., 2009; Graham et al., 2011) and attentional bias for high-calorie food in a fed state, predicts greater *ad lib* food intake (Nijs, Muris, Euser, & Franken, 2010b; Werthmann, Field, Roefs, Nederkoorn, & Jansen, 2014) and future weight gain (Calitri, Pothos, Tapper, Brunstrom, & Rogers, 2010). Obese versus lean individuals likewise show greater recruitment of motor response regions when exposed to high-calorie food images (Brooks et al., 2013; Jastreboff et al., 2013), suggesting an elevated motor approach tendency.

The finding that elevated reward and attention region responsivity predicts future weight gain converges with evidence from controlled trials that weight loss reduces reward region (e.g., parahippocampal gyrus, parietal cortices, putamen, insula, visual cortex) responsivity to highcalorie food images (Cornier, Melanson, Salzberg, Bechtell, & Tregellas, 2012; Deckersbach et al., 2014; Rosenbaum, Pavlovich, Leibel, & Hirsch, 2008), an effect not impacted by acute hunger. Weight loss has also been associated with concurrent reductions in food preference ratings for high-calorie foods relative to changes observed in waitlist controls (Deckersbach et al., 2014). Yet it is important to acknowledge that these effects might be driven by changes in afferent regulation pathways (e.g., glucose/insulin signaling from fat tissue).

The above findings imply that some individuals may show an elevated propensity to associate reward from high-calorie food intake with cues repeatedly paired with such food reward, which drives elevated responsivity of reward regions to food cues. As noted, animal experiments indicate that after repeated pairings of palatable food receipt and cues that predict palatable food receipt, dopamine signaling increases in response to predictive cues but decreases in response to food tastes (Schultz et al., 1997; Tindell et al., 2004; Tobler et al., 2005). One functional MRI study documented an increase in caudate response to cues predicting impending milkshake receipt over repeated pairings of the predictive cues and milkshake receipt, demonstrating a direct measure of *in vivo* cue-reward learning in humans (Burger & Stice, 2014). This effect was not impacted by hunger, as in theory the association would be more rapid in a fasted state. Further, that study observed a simultaneous decrease

in putamen and ventral pallidum response during milkshake receipt that occurred over repeated pairings of the cue and milkshake receipt, mirroring the reduction in dopamine release in response to food reward after it is repeatedly paired with a cue that signals impending food receipt (Zellner & Ranaldi, 2010). The reduction in putamen and ventral pallidum signal may reflect reinforcer satiation. Another human fMRI study found an increase in striatal response to visual cues that predict the possibility of winning money, and a simultaneous decrease in striatal response to winning money, as participants played a slot-machine game (Shao, Read, Behrens, & Rogers, 2013). Critically, participants who exhibited the greatest escalation in ventral pallidum responsivity to cues and those who exhibited the greatest decrease in caudate response to milkshake receipt showed significantly larger increases in BMI over 2-year follow-up ($r = .39$ and $-.69$ respectively; Burger & Stice, 2014). These results provide evidence that there are important individual differences in food cue-reward learning and food reinforcer satiation that may give rise to elevated reward region responsivity that underlies the incentive sensitization process. These individual difference factors may explain why only some people show obesity onset in response to the current obesogenic environment in western cultures.

In sum, heightened reward region responsivity to food cues or anticipated receipt predicted future weight gain and poorer response to a weight loss intervention. Studies also found that weight loss is associated with a reduction in reward region responsivity to high-calorie food images. Another study found that there are individual differences in cue-reward learning and food reinforcer satiation, and that individuals who show the most potent reward-cue learning and food reinforcer satiation show elevated future weight gain. Findings from these prospective studies and randomized experiments provide strong support for the incentive sensitization theory of obesity.

Reward Surfeit Theory of Obesity

It has been theorized that individuals who show greater reward region responsivity to food intake, which is presumably an inborn characteristic, are at elevated risk for overeating (Davis, Strachan, & Berkson, 2004; Loxton & Dawe, 2006), which we refer to as the reward surfeit model of overeating. An initial heightened reward-related response to palatable food, as proposed here, might amplify the aforementioned Pavlovian conditioning process.

Studies evaluating risk factors for obesity have generated findings consistent with the thesis that elevated reward region response to high-calorie food receipt, rather than elevated reward region response to cues for high-calorie foods or decreased reward region response to high-calorie food receipt, constitutes the initial vulnerability factor that increases risk for initial overeating. Healthy weight adolescents at high- versus low-risk for future weight gain based on parental obesity status showed greater activation of regions implicated in encoding reward (caudate, putamen, OFC) in response to receipt of high-calorie food and monetary reward, but did not show elevated reward region response to visual cues signaling impending tastes of high-calorie foods or impending monetary reward (Stice et al., 2011). An examination of an independent sample likewise found that healthy weight adolescents with versus without parental obesity showed elevated caudate response of tastes of a high-sugar food, but not to images of high-calorie foods (Shearrer, Stice & Burger, 2018). These results

converge with evidence that individuals who rate high-calorie foods as high versus low in pleasantness show greater future weight gain (e.g., Salbe et al., 2004).

Prospective studies have examined the relation between neural response to receipt of high-calorie foods and future weight gain. Elevated response to high-calorie milkshake tastes in the midbrain, thalamus, hypothalamus, ventral pallidum, and nucleus accumbens in 15 adults predicted elevated weight gain over 1-year follow-up (Geha et al. 2013). These results appear to converge with evidence that elevated resting state activation in reward regions (e.g., vmPFC) predicted future weight gain (Dong et al., 2014). However, three larger studies did not find a main effect between reward region response to high-calorie food receipt and future weight gain (Stice, Spoor, Bohon, & Small, 2008a; Stice, Burger, & Yokum, 2015; Sun et al., 2015). There is also evidence that individuals who show greater recruitment of reward-related regional response (e.g., striatum) to tastes of high-calorie milkshakes show greater future weight variability, operationalized as greater observed deviation of participants BMI over time around their average BMI (Winter et al., 2017). Weight variability may better capture the cumulative effects of repetitive periods of weight gain, which are often countered by periods of weight loss.

Elevated reward region responsivity has also been theorized to increase risk for substance abuse (Davis & Claridge, 1998). Consistent with this thesis, non-substance using adolescents at high- versus low-risk for future substance use disorders, based on parental substance use disorder, showed greater activation of a key reward region (midbrain) in response to receipt of high-calorie food (Stice & Yokum, 2014). Further, elevated reward region responsivity (caudate, putamen) in response to monetary reward predicted future substance use onset (Stice, Yokum, & Burger, 2013). These data suggest that reward region hyper-responsivity may increase risk for a range of appetitive problems and that there may be parallels in neural vulnerability factors that increase risk for obesity and substance use.

In sum, healthy weight adolescents at high-risk for future weight gain by virtue of parental obesity showed greater reward region responsivity to palatable food receipt and monetary reward than their low-risk counterparts in two studies, individuals who evidenced elevated reward region responsivity to palatable food receipt showed greater future weight gain, though this finding did not replicate in three other studies, and greater resting state activation in a network including a region implicated in reward processing predicted future weight gain. Thus, extant findings provide moderate support for the reward surfeit theory of obesity.

Reward Deficit Theory of Obesity

The reward deficit model of obesity posits that individuals with lower sensitivity of dopamine-based reward regions overeat to compensate for this reward deficiency (Wang et al., 2002). This theory was based on evidence that drugs that block dopamine D2 receptors increase appetite and result in weight gain, whereas drugs that increase brain dopamine concentrations reduce appetite and produce weight loss (Wang et al., 2001). However, all psychoactive drugs, including stimulants, barbiturates, benzodiazepines, opioids, and marijuana, increase dopamine signaling in reward circuitry (Wise & Rompre, 1989), but only stimulants are associated with weight loss. Further, “dopaminergic” drugs, such as

amphetamine, increase neurotransmission of dopamine, serotonin, norepinephrine, epinephrine, histamine, acetylcholine, opioids, and glutamate (Eiden & Weihe, 2011; Loseth, Ellingsen, & Leknes, 2014; Miller, 2011), making it difficult to conclude that the increase in dopaminergic signaling in particular causes weight loss. Likewise, "antidopaminergic" drugs affect neurotransmission of dopamine and serotonin, also show affinity for adrenergic, opioidergic, and glutamate receptors (Meltzer, 2002; Miller, 2009), making it difficult to conclude that it is the decrease in dopamine signaling that cause weight gain. Indeed, a randomized trial that directly compared the effects of haloperidol, an antipsychotic with very high affinity for dopamine D2 receptors, to clozapine and olanzapine, which are atypical antipsychotic medications with lower affinity for dopamine D2 receptors, found that only the atypical antipsychotics resulted in weight gain; haloperidol did not (Krakowski, Czobor, & Citrome, 2009).

Although some cross-sectional data are consistent with the thesis that obese versus lean individuals show less activation of reward circuitry from high-calorie food intake (Babbs et al., 2013; Frank et al., 2012; Green et al., 2011; Stice et al., 2008a, b), repeated-measures fMRI studies with humans and experiments with animals suggest that overeating causes a reduction in reward region responsivity. Young women who gained weight over a 6-month period showed a reduction in striatal responsivity to palatable food receipt versus women who remained weight stable (Stice, Yokum, Blum, & Bohon, 2010a). Further, experimentally induced consumption of a high sugar beverage caused decreases in striatal response to tastes of that beverage (Burger, 2017). These finding converge with numerous overfeeding experiments with animals; rats randomized to overeating conditions that result in weight gain versus control conditions show down-regulation of post-synaptic D2 receptors, and reduced D2 sensitivity, extracellular dopamine levels in the nucleus accumbens and dopamine turnover, and lower sensitivity of dopamine reward circuitry to food intake, electrical stimulation, amphetamine administration, and potassium administration (Bello et al., 2002; Davis et al., 2008; Geiger et al., 2009; Kelley et al., 2003; Johnson & Kenny et al., 2010; Thanos et al., 2008). One experiment randomized rats to a 40-day period of unlimited access to a high-calorie diet, to limited access to a high-calorie diet, or unlimited access to rat chow; they then randomized rats in each condition to exposure to a light cue that was associated with a foot shock or the light cue only, finding that on a subsequent test day, exposure to the light cue reduced caloric intake in rats that had experienced limited access to the high-calorie diet or unlimited access to the chow diet, but not in those that had previously had unlimited access to the high-fat/sugar diet (Johnson & Kenny, 2010). These authors concluded that habitual intake of energy dense diets may induce a compulsive-style of eating that is resistant to subsequent punishment learning. These findings were replicated in a study by an independent team (Thompson et al., 2017), which also found that intermittent access to a high-calorie diet resulted in decreased spine density in basal dendrites of layer II/III lateral OFC neurons, suggesting that inhibitory inputs to lateral OFC pyramidal neurons are diminished in rats with extended access to a cafeteria diet. Pigs randomized to a weight gain intervention versus a stable weight condition showed reduced resting activity in the midbrain and nucleus accumbens (Val-Laillet et al., 2011). The reduced dopamine signaling capacity appears to occur because habitual intake of high-fat diets decreases synthesis of oleoylethanolamine, a gastrointestinal lipid messenger

(Tellez et al., 2013). Experiments also indicate that humans randomized to consume high-calorie foods daily over 2–12 week periods report reduced "liking" of the foods relative to baseline and control high-calorie foods not consumed daily (Clark et al., 2010; Hetherington et al., 2000; 2002; Temple et al., 2009; Tey et al., 2012).

The evidence that weight gain is associated with down-regulation of dopamine-based reward circuitry dovetails with evidence that weight loss increases D2 receptor availability in humans (Steele et al., 2010) and rats (Thanos et al., 2008), and responsivity of reward circuitry to food cues (Cornier et al., 2012; Deckersbach et al., 2014; Rosenbaum et al., 2008). However, one study reported that weight loss was associated with a reduction in D2 receptor availability (Dunn et al., 2010); the inconsistent findings are likely to due the very small samples used in PET studies.

One experiment found that intake of high-fat/high-sugar food resulted in down regulation of striatal D1 and D2 receptors in rats relative to isocaloric intake of low-fat/low-sugar rat chow (Aliso et al., 2010), implying that it is intake of energy dense foods versus a positive energy balance *per se* that causes plasticity of reward circuitry. Another study found that mice that received chronic intra-gastric infusion of fat showed reduced striatal dopamine signaling from food intake relative to chow fed weight-matched control mice (Tellez et al., 2013), providing further evidence that habitual consumption of fat can reduce dopamine response to food intake, independent of weight gain.

The evidence that overeating results in down-regulation of dopamine-based reward circuitry seems to converge with data suggesting that habitual substance use, which also causes acute increases in dopamine-signaling, likewise leads to down-regulated reward circuitry. For instance, lower dopamine release in the nucleus accumbens in response to methylphenidate has been observed in cocaine-dependent and alcohol-dependent individuals relative to healthy controls (Volkow et al., 1997, 2007). Indeed, even adolescents with a relatively short history of substance use showed less caudate response to monetary reward than adolescents who had not initiated substance use (Stice et al., 2013).

Given that animals that have shown down-regulation of reward circuitry because of habitual drugs use will work to keep dopamine levels in the nucleus accumbens above a certain level (Wise et al., 1995; Ranaldi et al., 1999), Geiger and associates (2009) speculate that rats that have experienced diet-induced down-regulation of dopamine circuitry may overeat to increase dopamine signaling. However, a study found that mice in which reduced striatal dopamine signaling from food intake was experimentally induced through chronic intra-gastric infusion of fat worked *less* for acute intra-gastric infusion of fat and consumed *less* rat chow *ad lib* than control mice (Tellez et al., 2013). These animal findings converge with evidence that experimentally induced dopamine depletion in humans resulted in decreased hunger ratings and less *ad lib* caloric intake relative to the control condition, though the later effect was only marginal because of the small sample (Hardman, Herbert, Brunstrom, Munafo, & Rogers, 2012). Further, genetically engineered dopamine-deficient mice are unable to sustain appropriate levels of feeding and dysregulation of dopamine signaling in the dorsal striatum in particular is sufficient to induce hypophagia (e.g., Sotak et al., 2005; Zhou & Palmiter, 1995). These data converge with the finding that experimental

administration of 6-hydroxydopamine, a neurotoxin that selectively destroys dopaminergic and noradrenergic neurons, at any of several points along the nigrostriatal dopamine pathway between the substantia nigra and the caudate-putamen results in severe aphasia (Robbins & Everitt, 1999). These findings seem incompatible with the notion that an induced down-regulation of dopamine reward circuitry leads to compensatory overeating.

Prospective fMRI studies that have examined neural responsivity that predicts future weight gain have also produced little support for the reward deficit theory. None of the 8 prospective studies that examined the relation of BOLD response to high-calorie palatable food images/cues, anticipated palatable food receipt, and palatable food receipt to future weight gain reviewed above found a main effect between reduced reward region responsivity to these food stimuli and greater future weight gain (Demos et al., 2012; Geha et al. 2013; Stice et al., 2008a, 2010b, 2015; Sun et al., 2015; Yokum et al., 2011, 2014). Further, lean youth at risk for future obesity by virtue of parental obesity show hyper-responsivity of reward regions to palatable food receipt and monetary reward, and no evidence of hypo-responsivity or reward regions (Shearrer et al., 2018; Stice et al., 2011).

In sum, research provides little prospective or experimental support for the thesis that individuals who show reduced responsivity of reward circuitry to food stimuli overeat to compensate for this deficit. Adolescents at high- versus low-risk for future weight gain showed elevated reward region responsivity to food and no evidence of blunted reward region response and none of the eight prospective studies found a main effect wherein lower reward region response to food stimuli predicted future weight gain. Indeed, most of these prospective studies found that *elevated responsivity of reward circuitry*, including the amygdala, midbrain, ventral pallidum, nucleus accumbens, and striatum, to food images/cues and anticipated palatable food receipt predicted future weight gain. Moreover, experimentally induced down-regulation of dopamine response to fat intake in mice reduced caloric intake and the motivational value of high-calorie food compared to control mice, experimentally-induced dopamine depletion was associated with less *ad lib* food intake in humans, and dopamine-deficient mice are unable to sustain appropriate levels of feeding.

Inhibitory Control Deficit Theory of Overeating

It has been proposed that individuals with inhibitory control deficits, and lower responsivity of brain regions implicated in inhibitory control, are more sensitive to food cues and more vulnerable to the pervasive temptation of appetizing foods in our environment, which increases overeating (Nederkoorn et al., 2006). Trait impulsivity putatively results in greater sensitivity to reward-predictive cues, which may contribute to elevated food intake (Diergaarde et al., 2009).

Inhibitory control deficits in response to high-calorie foods in delay discounting tasks, which reflects an immediate reward bias, has reliably predicted future weight gain (Evans, Fuller-Rowell, & Doan, 2012; Francis & Susman, 2009; Schlam, Wilson Shoda, Mischel, & Ayduk, 2013; Seeyave et al., 2009). Similar results have emerged from studies that examined self-report measures of inhibitory control (Anzman & Birch, 2009; Duckworth, Tsukayama, & Geier, 2010; Sutin, Ferrucci, Zonderman, & Terracciano, 2011). Functional connectivity

between weight discordant twins and matched, unrelated samples revealed that a network compromised of gustatory processing regions, a visual processing network, and the default mode network all correlate with weight status (Sadler et al., 2018). This study also found that lower weight was associated with greater integration of regions that encode reward learning and executive control, and underpin hedonically motived behaviors. It is possible that differences in network connectivity may contribute to better behavioral control when lean individuals are faced with highly palatable foods. Individuals with inhibitory control deficits show poorer response to weight loss treatment and poorer weight loss maintenance (Nederkoorn et al., 2007; Weygandt et al., 2013; Weygandt et al., 2015), though the former effect did not emerge in one study (Jonsson, Bjorvell, Levander & Rossner, 1986). Further, rats that showed behavioral disinhibition in response to food reward on a serial reaction time task exhibited greater future sucrose seeking behaviors and sensitivity to sucrose-associated stimuli after extinction, relative to rats that exhibited behavioral inhibition (Diergaarde et al., 2009).

With regard to neuroimaging findings, obese versus lean teens showed less activation of prefrontal regions (dorsolateral prefrontal cortex [dlPFC], ventral lateral prefrontal cortex [vlPFC]) when trying to inhibit responses to high-calorie food images and behavioral evidence of reduced inhibitory control (Batterink et al., 2010), though participants who showed less recruitment of inhibitory regions did not show elevated future weight gain. Another study found that participants who showed less recruitment of inhibitory control regions (inferior, middle, and superior frontal gyri) during difficult versus easy choices on a delay-discounting task showed elevated future weight gain (Kishinevsky et al., 2012). A third prospective study found that individuals who showed less activation of the pre-supplementary motor area in response to tastes of milkshake, which might reflect lower inhibition of motor response to high-calorie food, showed greater future weight gain (Stice & Yokum, 2018). Further, individuals that showed less recruitment of inhibitory control regions (dorsolateral prefrontal cortex) during a delay discounting task showed significantly less weight loss in response to weight loss treatment (Weygandt et al., 2013) and less weight loss maintenance over a 1-year follow-up (Weygandt et al., 2015). These results converge with evidence that obese versus lean adults showed less grey mater volume in the prefrontal cortex (Pannacciulli et al., 2006), a region that modulates inhibitory control, and with a marginal trend for reduced grey matter volume in the prefrontal cortex to predict weight gain over 1-year follow-up (Yokum, Ng, & Stice, 2012). Further, lower dlPFC response to high-calorie food images predicted greater *ad lib* food intake over the next 3 days (Cornier et al., 2010) and individuals reporting chronic stress showed less recruitment of frontal regions in response to images of high-calories foods as well as greater *ad lib* caloric intake (Tryon, Carter, DeCant, & Laugero, 2013). The findings from the latter two studies are noteworthy because they emerged in paradigms lacking a behavioral response component. These findings may be explained by the fact that the primary motor area received a very dense innervation from dopamine-containing fibers originating in the midbrain (Berger, Gaspar, & Verney, 1991). Indeed, participants have shown activation of motor regions, as assessed via electromyography, in response to palatable food images (Gupta & Aron, 2011).

It is noteworthy that elevated impulsivity has also predicted future onset of (Ernst et al., 2006; Leeuwen et al., 2011; Malmberg et al., 2012; McGue et al., 2001) and increases in

substance use (Krank et al., 2011; Stice et al., 1998). Further, adolescents who showed less prefrontal inhibitory region recruitment during a go/no-go task were more likely to show onset of heavy alcohol use (Norman et al., 2011).

It is important to note that there is emerging evidence from animal experiments that habitual intake of high-calorie foods may contribute to increased impulsivity, which may drive a further escalation in overeating. Specifically, experiments have found that rats randomized to consume a high-calorie diet versus a low-calorie diet, which results in greater weight gain and greater overeating, showed greater impulsivity, operationalized by an immediate reward bias for high-calorie foods, after receiving haloperidol (Boomhower & Rasmussen, 2014; Roberson et al., 2017, Roberson & Rasmussen, 2017).

In sum, individuals with a preference for immediate food reward show elevated weight gain, with similar results emerging from studies that used self-report measures of inhibitory control. Data also indicate that individuals with inhibitory control deficits show a poorer response to weight loss treatment and poorer maintenance of weight loss after treatment. One imaging study found that individuals who show less recruitment of inhibitory control regions in tasks that require inhibition showed elevated future weight gain, but this effect did not emerge in a second study that used a different inhibitory control paradigm. One study suggested that individuals who exhibited lower recruitment of a region implicated in motor inhibition in response to high-calorie beverage receipt showed greater future weight gain, and another found that individuals that showed less recruitment of inhibitory control regions during a delay discounting task showed significantly less weight loss in response to a negative energy balance diet. Collectively, these data provide prospective support for the inhibitory control deficit theory of obesity, though many of the predictive effects were small and findings were somewhat mixed.

Genetic Predisposition for Reward-Related Obesity

There are also genetic findings that appear to provide support for various etiologic theories introduce previously. First, individuals with a genetic propensity for elevated dopamine signaling capacity in reward circuitry showed elevated future weight gain in three samples, as well as significantly less weight loss in response to obesity treatment (Yokum, Marti, Smolen, & Stice, 2015). That study examined a multilocus score because it relates more strongly to reward region responsivity than the individual alleles used to calculate the composite genetic risk score (Nikolova, Ferrel, Manuck, & Hariri, 2011; Stice et al., 2012). Theoretically, this is because the greater number of these genotypes, regardless of the particular combination, the greater the dopamine signaling. These findings appear consistent with the reward surfeit model of obesity.

There are also some interactive findings that warrant mention. Two studies found significant interactions wherein elevated caudate response to milkshake receipt predicted future weight gain for adolescents with a genetic propensity for greater dopamine signaling by virtue of possessing the *TaqIA* A2/A2 allele, but lower caudate response predicted weight gain for adolescents with a genetic propensity for lower dopamine signaling by virtue of possessing one or more *TaqIA* A1 allele (Stice et al., 2008a; Stice et al., 2015). However, we were

unable to replicate this interactive effect in a third prospective study (Stice & Yokum, 2018). Another study found a significant interaction wherein elevated amygdala response to milkshake receipt predicted future weight gain for adults with a genetic propensity for greater dopamine signaling by virtue of possessing the *TaqIA* A2/A2 allele, but lower amygdala response predicted weight gain for adults with a genetic propensity for lower dopamine signaling by virtue of possessing one or more *TaqIA* A1 allele (Sun et al., 2015). However, this study likewise did not replicate the interaction between *TaqIA* allele status and caudate response to milkshake receipt in the prediction of future weight gain. Another study found that adolescents who showed elevated striatal and OFC response to palatable food images and who had a genetic propensity for greater dopamine signaling due to possessing an A2/A2 *TaqIA* allele showed greater future weight gain, whereas adolescents who showed weaker putamen and OFC response to palatable food images and who had a genetic propensity for weaker dopamine signaling due to possessing the *TaqIA* A1 allele also showed greater future weight gain (Stice et al., 2010b). Further, individuals with both the fat mass and obesity-associated (FTO) gene and *TaqIA* A1 polymorphism are insensitive to negative reward learning, exhibit reduced connectivity between the nucleus accumbens and medial prefrontal cortex, and reduced connectivity between the ventral tegmental area (VTA) and substantia nigra in a "dose by gene response" (Sevgi et al., 2015). The interactive effects observed in these studies suggest the possibility of qualitatively distinct reward surfeit and reward deficit pathways to obesity. It is possible that the reward surfeit model may apply to individuals with a genetic propensity for greater dopamine signaling capacity and that the reward deficit model may apply to those with a genetic propensity for weaker dopamine signaling. These data may imply that too much or too little dopamine signaling capacity and reward region responsivity may both increase risk for overeating, potentially because each perturbs homeostatic processes that maintain a balance between caloric intake and caloric expenditure. There are other examples of such inverted U-shaped relations between neurotransmitters and neural function, such as the evidence that too little or too much epinephrine and norepinephrine impair memory formation (Eichenbaum et al., 1999).

Dynamic Vulnerability Model of Obesity

Our team has attempted to synthesize the above theories into a unifying etiologic model regarding neural vulnerability factors that increase risk for overeating, and changes in neural responsivity that result from overeating that may contribute to future escalations in caloric intake. This working model, referred to as the dynamic vulnerability model (Stice & Yokum, 2016), is summarized in Figure 2. Thick black arrows represent well-established relations and thinner black arrows represent relations with a more provisional degree of empirical support.

According to this integrative model, individuals who show greater responsivity of reward regions to high-calorie foods are at increased risk overeating and consequent weight gain, consistent with the reward surfeit model of obesity. This is based on evidence that adolescents at high- versus low-risk for future weight gain because of parental obesity showed greater responsivity of reward regions to palatable food tastes (Shearrer et al., 2018; Stice et al., 2011), as well as the evidence that elevated reward region response to high-calorie food predicted future weight gain (Geha et al., 2013). Regular consumption of high-

calorie foods is thought to result in an increase in the valuation of cues that predict high-calorie food availability via the conditioning process described in the incentive sensitization model of obesity, and elevated reward region response to cues for high-calorie food availability is theorized to increase risk for overeating when these cues are encountered. These predictions are based on animal experiments that show that regular intake of high-calorie foods results in increased incentive value of cues that predict high-calorie food availability (Schultz et al., 1997; Tindell et al., 2004; Tobler et al., 2005), on evidence that a period of overeating results in elevated reward region responsivity to food cues compared to humans who do not overeat (Stice & Yokum, 2016), and on evidence that elevated reward region response to food cues predicts future weight gain (Demos et al., 2012; Stice et al., 2010b, 2015; Sun et al., 2015; Yokum et al., 2011, 2014). Based on the aforementioned studies, hyper-responsivity of reward valuation regions to food cues appears to be a more potent driver of overeating than the initial hyper-responsivity of reward regions to palatable food intake. With this in mind, obesity can be conceptualized as resulting from aberrant reinforcement learning processes. Theoretically, these reinforcement-based learning processes are more likely for individuals with a propensity for reward cue learning and food reinforcement satiation, based on evidence that elevated reward-cue learning and food reinforcement satiation are associated with habitual consumption (Burger & Stice, 2014; Burger 2017).

The dynamic vulnerability model also hypothesizes: 1) that a genetic propensity for higher dopamine signaling directly increases risk for overeating, and 2) moderates the predictive effects of greater reward region responsivity to high-calorie food tastes and greater reward valuation region responsivity to food cues on future weight gain. This model posits that individuals who show stronger reward region responsivity to food intake will exhibit greater weight gain if they have a genetic propensity for elevated dopamine signaling, but individuals who show a weaker reward region responsivity to food intake will exhibit greater weight gain if they have a genetic propensity for weaker dopamine signaling. These predictions are based on the evidence that individuals with a genetic propensity for greater dopamine signaling showed greater future weight gain in three samples (Yokum et al., 2015) and on the interactions observed in three out of four studies (Stice et al., 2008a, 2015, 2018; Sun et al., 2015) which imply that there may be two qualitatively distinct pathways to obesity that conform to the reward surfeit and reward deficit models.

The emergence of habitual overeating is theorized to lead to a reduction in dopamine, D2 receptors, D2 receptor gene expression, and striatal responsivity to palatable food intake, primarily based on animal overfeeding experiments (e.g., Davis et al., 2008; Geiger et al., 2009; Johnson & Kenny et al., 2010; Thanos et al., 2008; Vucetic et al., 2012). Human imaging studies show similar effects where experimental manipulation of food intake caused decreases in striatal response to receipt (Burger 2017) and weight gain was associated with a decrease in striatal response to palatable food (Stice et al., 2010a). The emergence of habitual overeating is also thought to increase incentive valuation region responsivity to food cues repeatedly associated with palatable food intake, in line with the incentive sensitization model. Conditioning experiments with primates and rodents have documented an increase in dopamine signaling in reward regions, such as in the midbrain dopamine neurons in response to stimuli repeatedly paired with palatable food receipt (Mackintosh, 1974;

Mirenowicz & Schultz, 1994; Stuber et al., 2008; Zellner & Ranaldi, 2010), which has been documented acutely using neuroimaging with humans in one study (Burger & Stice, 2014). This prediction is also supported by evidence that weight gain in humans was associated with an increased striatal response to cues for high-calorie food receipt (Stice & Yokum, 2016).

Available findings also suggest that a bias for immediate reward also constitutes an important risk factor for overeating and subsequent weight gain (e.g., Evans et al., 2012; Schlam et al., 2013; Seeyave et al., 2009). Given the evidence that a bias for immediate food reward in childhood predicts future weight gain over very long-term follow-up, this may constitute another key initial vulnerability factor for obesity. The development of reflexive, immediate (habit-like) bias to food cues has been observed in humans, where daily consumption of a high-sugar beverage with a logo resulted in a decrease in reaction time toward that logo (Burger 2017). Notably, this decrease was correlated to decreases in the prefrontal cortex during logo exposure. As such, this vulnerability factor presumably has a neural basis, but few neuroimaging studies with humans have tested whether reduced recruitment of inhibitory regions in response to tasks involving inhibition to food stimuli predicts future weight gain. This immediate reward bias may contribute to the initial emergence of habitual overeating that contributes to the incentive sensitization process. One might hypothesize that elevated reward region responsivity to palatable food and a bias for immediate reward might interact in an amplifying fashion in the prediction of overeating. However, to date no prospective data has tested this interactive hypothesis.

Clinical Implications

Results from this review have a several implications for the prevention and treatment of obesity. With regard to the former, results imply that interventions that reduce habitual intake of high-calorie foods during childhood and adolescence might reduce elevated incentive valuation region responsivity to food cues that appears to drive overeating. A related policy implication is that reducing the presence of cues for high-calorie foods, such as advertisements for fast foods, should also reduce overeating in those with this vulnerability factor. Further, prevention programs that promote executive function and inhibitory control, which includes resisting temptation (e.g., Diamond, Barnett, Thomas, & Munro, 2007), might reduce the immediate reward bias that increases risk for overeating.

In terms of treatment implications, response training might prove useful in reducing valuation of food cues and promoting inhibitory responses to food cues (Stice, Lawrence, Kemps, & Veling, 2016). Response training experiments show that repeatedly presenting high-calorie food images with signals indicating that participants should withhold a prepotent behavioral response in stop-signal or go/no-go tasks decreases later consumption of that food versus high-calorie foods not repeatedly paired with inhibitory signals (Houben, 2011; Houben & Jansen, 2011; Lawrence et al., 2014). There is also evidence that response training produces weight loss (Lawrence et al., 2014; Veling, Koningsbruggen, Aarts, & Stroebe, 2014). Experiments have also found that completing computer-based tasks that train attention away from high-calorie foods using modified dot-probe tasks may also reduce valuation of high-calorie food cues. Specifically, participants who complete attend-away

from high-calorie food images versus attend-to high-calorie food images reduces attentional bias for high-calorie foods, high-calorie food craving, and high-calorie food intake versus participants in the chocolate respond-toward training condition (Kakoschke et al. 2014; Kemps et al., 2014a 2014b; Kemps, et al., 2015). A pilot trial tested the hypothesis that a multi-faceted food response and attention training with personalized high- and low- calorie food images would produce changes in behavioral and neural responses to food images and body fat compared to a control training with non-food images among community-recruited overweight/obese adults (Stice, Yokum, Veling, Kemps, & Lawrence, 2017). Compared to changes observed in controls, completing the intervention was associated with significant reductions in reward and attention region response to high-calorie food images, behavioral evidence of learning, reductions in palatability ratings and monetary valuation of high-calorie foods, and greater body fat loss over a 4-week period, though body fat effects were not significant by 6-month follow-up.

Another treatment implication is that it might be possible to use brain imaging to predict response to obesity treatment, which could allow clinicians to focus on those individuals most likely to show a positive response to weight loss treatment. Individuals who show less reward and attention region response to high-calorie food images (Murdaugh et al., 2012) and individuals who show greater recruitment of inhibitory control regions (dorsolateral prefrontal cortex) during a delay discounting task (Weygandt et al., 2013, 2015) exhibited a more positive response to behavioral weight loss treatment. Likewise, individuals with a genetic propensity for lower dopamine signaling capacity in reward circuitry showed a more positive response to behavioral weight loss treatment (Yokum et al., 2015).

The evidence of individual variability in risk factors describe previously suggests that tailored treatments might improve the overall yield of treatment efforts (Klonoff, 2009). For individuals who show elevated reward region response to energy dense food receipt, it might be optimal to prescribe Naltrexone, which attenuates reward region responsivity (Murrey et al., 2014). Interestingly, bromocriptine (Cycloset™), a dopamine D2 receptor agonist used for the treatment of type 2 diabetes (T2DM) may offer another unique treatment strategy. Notably, presence of the *TaqIA* A1 allele is disproportionately prevalent in the T2DM population (Barnard et al., 2009; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991). In T2DM treatment, bromocriptine is thought to augment low hypothalamic dopamine and suppress hepatic glucose production, lipolysis and lipogenesis, ameliorating T2DM independent of insulin action. In support of this mechanism, destruction of hypothalamic dopamine neurons causes insulin resistance, and insulin resistance is associated with low dopamine levels in animal models (Albert & Anthony, 1998; Luo, Liang, & Cincotta, 1999). In theory, pharmacological augmentation of low dopamine D2 also may impact hedonic responsivity to food stimuli (e.g., ad lib food intake) and this effect may be amplified in those with the *TaqIA* A1 allele. While no publications report directly assessing this in humans, bromocriptine impacts hedonic aspects of food intake in animal models, where the agonist increased food reinforcement and decreased chow intake (Thanos et al., 2011). Further, *TaqIA* status significantly moderated the effectiveness of acute bromocriptine administration on striatal functioning and behavioral performance during a reward/punishment gambling-style task where participants won and lost theoretical money (Kirsch et al., 2006). Specifically, presence of a TaqIA A1 allele, ‘corrected’ striatal response and

performance to be equivalent with those with the A2/A2 allele. Although bromocriptine treatment may not result in clinical meaningful weight loss, as individual risk factors become more reliably identified, these can be capitalized on for new opportunities for personalized treatments.

The evidence that habitual intake of high-calorie foods results in a simultaneous increase in reward region responsivity to food cues and reduced reward region responsivity to high-calorie food tastes from studies with humans (Stice et al., 2010, 2016) and other animals (e.g., Davis et al., 2008; Geiger et al., 2009; Johnson & Kenny et al., 2010; Thanos et al., 2008) is striking. Habitual use of psychoactive substances appears to induce parallel neural changes with regard to reward region response to substance use cues and receipt (e.g., Due et al., 2002; Myrick et al., 2004; Tapert et al., 2003; Volkow et al., 1997, 2007). These findings suggest that there are parallels in how reward circuitry responds to habitual engagement in activities that are hedonically pleasurable, and that response may increase the likelihood of engaging in those activities more in the future (Ivezaj et al., 2017). The fact that relapse rates from obesity treatment exceed 90% within 2-years likewise implies that a period of overeating markedly increases the likelihood of continued overeating in the future. Although it is tempting to suggest that high-calorie food may be addictive, it is important to note that many people who consume high-calorie foods do not experience habitual overeating of those foods, just as most people who smoke cigarettes do not become regular smokers. This suggests that future research is needed is to investigate individual difference factors that increase risk for habitual overconsumption of high-calorie foods (Ivezaj et al., 2017).

Limitations

The reproducibility of scientific results is of increased concern in recent years, prompting a focus on the reliability and false positive likelihood of findings. This is particularly relevant to neuroimaging, as methodological constraints of imaging research can contribute to concerns. These factors include general study design that may inadvertently introduce bias, low statistical power, and inconsistencies in data collection approaches, for example whether participants are fed or fasted during the scan, the time of day of the scan) as well as differences in analytic methods.

Hardware and data collection methods used in fMRI also can be problematic. Spatial and temporal resolution, or the spatial clarity of the images and how quickly it can assess repeated images respectively, is lacking. Further, fMRI is a measuring a proxy of cerebral blood flow (CBF) blood flow, not CBF/receptor binding itself. Head motion acts as a confound, and affects the researcher’s ability to test hypotheses.

The elimination of scans/runs/subjects due to motion also contributes to a pervasive issue in fMRI research: inadequate power. The most common approach to neuroimaging analysis involves mass univariate testing in which a separate hypothesis test is performed for each voxel. In mass univariate testing in fMRI, the false positive rate will be inflated if there is no correction for multiple tests. The problem of multiplicity in neuroimaging analysis was recognized very early, and the past 25 years have seen the development of well-established

and validated methods for correction of multiple comparisons and false-discovery rates in neuroimaging data.

Utilizing brain response to investigate aspects of eating behavior and weight regulations brings forth a unique confound, specifically physiology and the metabolic processes that are known to act on brain response. The impact of excess fat tissue, circulating appetitive hormones, and insulin and blood glucose regulation on BOLD response is an infrequently discussed concern. Observation and manipulation of specific physiological states, e.g., leptin replacement, has been studied, yet in the larger body of literature, this point is rarely assessed (Burger & Burn, 2014).

Akin to the above, individual variability in insulin regulation relates to neural functioning and BOLD response, in particular dopamine functioning. Although best known for its action in glucose metabolism in the liver and muscle, insulin is critical within the CNS for glucose metabolism, satiety signaling, and possibly, reward signaling (Kroemer & Small, 2016; Murray et al., 2014). Insulin receptors are found within the hypothalamus and within the striatum, among other regions (Kroemer & Small, 2016; Murray et al., 2014b). Peripheral and central Insulin concentrations and receptor activity has been shown to influence dopamine metabolism, concentration, and receptor availability (Kroemer & Small, 2016). Insulin has been shown to decrease dopamine concentrations via up-regulation of dopamine transport synthesis in the VTA (Figlewicz, et al., 1994). The relation between dopamine and insulin appears to extend beyond the central nervous system, for example, at high levels, peripheral insulin was correlated with suppressed dopamine release (Potter et al., 1999).

The lack of assessment of appetitive hormones and insulin sensitivity is likely due to increased cost of the blood draws and blood processing as well as the participant burden. Nevertheless, these assessments are an important point for discussion when evaluating these theories. Frequently, paying close attention to other design consideration or relevant study hypotheses scan alleviate this concern. For example, use of repeated measure scans allows for control of within-subject variability; Study of eating behavior in non-overweight individuals (relative the examination of obese vs. healthy weight) provides an opportunity to control for alterations in neuroendocrine function that are associated with higher BMI.

Future Research Directions

Although the prospective studies reviewed above have advanced our understanding of the risk processes that predict future weight gain, perhaps the most important direction for future research is for additional research teams to conduct larger sample prospective studies on neural vulnerability factors that predict future overeating and weight gain, as independent replication is vital for confirming the reliability of the findings from the initial prospective studies. These new large-sample prospective studies would also provide a unique opportunity to test novel hypotheses, such as whether inhibitory control deficits interact in an amplifying fashion with elevated reward region responsivity to food tastes and food cues in the prediction of future weight gain.

It would be useful for large prospective studies to test whether individuals who show more pronounced food reward-cue learning, captured during an fMRI scan are at elevated risk for future weight gain, as well as whether elevated reward region response to palatable food predicts greater reward-cue learning. It would also be useful to conduct repeated-measures imaging studies to document that overeating that results in weight gain leads to greater reward region response to food cues, as suggested by the incentive sensitization model and animal experiments, because there is limited evidence regarding the processes that give rise to elevated reward region response to food cues.

Further, it will be important for future studies to test whether genotypes that affect dopamine signaling capacity moderate the relation of reward region responsivity to future weight gain. Future studies should also investigate whether these genotypes, alone or in combination in a multilocus score, predict future weight gain, based on the findings from Yokum and associates (2015). In addition, it might be useful for future studies to investigate whether a genetic propensity for greater opioid signaling predicts future weight gain and amplifies the relation between reward region responsivity and subsequent weight gain.

Conclusion

Early cross-sectional brain imaging studies that could not differentiate precursors from consequences of overeating and did not examine responsivity to food intake were inconclusive regarding neural vulnerability factors that might drive overeating. More recent prospective imaging studies have now begun to identify considerable insight into the neural vulnerabilities that predict future weight gain and have begun to document neural plasticity associated with overeating. Elevated response of brain regions implicated in reward (dopaminergic midbrain, nucleus accumbens) and incentive valuation (medial orbitofrontal cortex) in response to anticipatory and visual food cues have been found to predict future weight gain and poorer response to behavioral weight loss treatment. These findings converge with evidence that healthy weight adolescents at high- versus low-risk for future weight gain show greater reward region responsivity to receipt of high-calorie food, adolescents with a genetic propensity for greater dopamine signaling in reward circuitry showed greater weight gain, and adolescents who show more pronounced food reward-cue learning showed greater future weight gain. Although animal experiments and experimental and repeated-measures human imaging studies indicate that overeating reduces reward region response to high-calorie foods, reduced reward region responsivity is associated with lower caloric intake, converging with a general lack of evidence that weaker reward region responsivity in humans predicts future weight gain. Thus, prospective and experimental data provide strong support for the incentive sensitization theory of obesity, and moderate support for the reward surfeit theory, inhibitory control deficit theory, and dynamic vulnerability model of obesity. The predictive effects for reward region responsivity are relatively large, suggesting it will be important to continue to conduct research on the neural vulnerability factors that increase risk for future weight gain.

Acknowledgements

Support for this work was provided by National Institutes of Health grants DK-080760, DK092468, and DK-112762.

Bibliographies

Dr. Stice served as an assistant professor and associate professor at the University of Texas at Austin, and subsequently took a position as Senior Research Scientist at Oregon Research Institute. His research focuses on identifying risk factors that predict onset of eating disorders, obesity, substance abuse, and depression to advance knowledge regarding etiologic processes, including the use of functional neuroimaging. He also designs, evaluates, and disseminates prevention and treatment interventions for eating disorders, obesity, and depression. He has published 271 articles in high-impact outlets, including *Science*, *Psychological Bulletin*, *Archives of General Biological Psychiatry*, *American Journal of Clinical Nutrition*, and *Journal of Neuroscience.* He received a Career Award from the National Institutes of Health and a Distinguished Scientific Award for Early Career Contributions to Psychopathology from the American Psychological Association. He is currently an Associate Editor for *Journal of Consulting and Clinical Psychology.*

Dr. Burger served as a research associate at Oregon Research Institute and currently is an assistant professor at the University of North Carolina at Chapel Hill and faculty at the Biomedical Research Imaging Center. Specifically, his work has focused on the individual differences in hedonically motivated food intake, characteristics of food impact eating behavior via decision making and reward learning processes that leverage techniques such as functional neuroimaging, examination of explicit behavior, and appetitive hormones of gustatory stimuli as primary reinforcer. His experiences have led to novel discoveries about the underpinnings of aberrant functioning associated with habitual eating patterns and the development of obesity. During his time at UNC-CH, he has received 4 large grants as PI investigating these topics resulting in a total of 30 publications in prominent journals in nutrition, cognitive neuroscience as well as journals focus on specifically neuroimaging. He has received multiple early career awards and honors for contributions to obesity research. He has reviewed for high impact journals such as: *Cell Metabolism, Journal of American Medical Association (JAMA), Molecular Psychiatry, and Proceedings of the National Academy of Sciences (PNAS).*

Dr. Stice served as an assistant professor and associate professor at the University of Texas at Austin, and subsequently took a position as Senior Research Scientist at Oregon Research Institute. His research focuses on identifying risk factors that predict onset of eating disorders, obesity, substance abuse, and depression to advance knowledge regarding etiologic processes, including the use of functional neural imaging. He also designs, evaluates, and disseminates prevention and treatment interventions for eating disorders, obesity, and depression. For instance, he developed a dissonance-based eating disorder prevention program that has been implemented with over 4 million young girls in 139 countries. He has published 264 articles in high-impact outlets, including *Science*, *Psychological Bulletin*, *Archives of General Biological Psychiatry*, *American Journal of Clinical Nutrition*, and *Journal of Neuroscience.* He received a Career Award from the National Institutes of Health and a Distinguished Scientific Award for Early Career Contributions to Psychopathology from the American Psychological Association. He is currently an Associate Editor for *Journal of Consulting and Clinical Psychology.*

Dr. Burger currently serves as an assistant professor of nutrition at the University of North Carolina at Chapel Hill and is part of the faculty of the Biomedical Research Imaging Center. His primary area of research focuses on eating behavior, how it evolves, implicit drivers and explicit perceptions of food intake. Specifically, he studies how these aspects of ingestive behavior relate to habitual consumption, executive control and weight regulation. His lab also is interested in the impact of the current food environment on ingestive behavior. Dr. Burger examines these questions using direct and indirect measures of food intake, functional brain imaging techniques -- particularly functional magnetic resonance imaging (fMRI) -- and a variety of behavioral and self-report measures. He has published 40 articles in peer-reviewed publications and four book chapters.

References

Adise S, Geier C, Roberts N, White C, & Keller K (2018). Is brain response to food reward related to overeating? A test of the reward surfeit model of overeating in children. Appetite, 128, 167–179. [PubMed: 29890186]

Ambrose L, Unterwald W, & van Bockstaele E (2004). Ultrastructural evidence for co-localization of dopamine D2 and micro-opioid receptors in the rat dorsolateral striatum. Anatomical Record Part A: Discoveries in Molecular, cellular, and evolutionary biology, 279, 583–591.

Anzman S, & Birch L (2009). Low inhibitory control and restrictive feeding practices predict weight outcomes. Journal of Pediatrics, 155, 651–656. [PubMed: 19595373]

Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, & Van Tol HH (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. Journal of Neurochemistry, 65, 1157–1165. [PubMed: 7643093]

Babbs RK, Sun X, Felsted J, Chouinard-Decorte F, Veldhuizen MG, & Small DM (2013). Decreased caudate response to milkshake is associated with higher body mass index and greater impulsivity. Physiology & Behavior, 121, 103–111. [PubMed: 23562867]

Batterink L, Yokum S, & Stice E (2010). Body mass correlates inversely with inhibitory control in response to food among adolescent girls: An fMRI study. Neuroimage, 52, 1696–1703. [PubMed: 20510377]

Balleine BW, Daw ND, & O'Doherty JP (2008). Multiple forms of value learning and the function of dopamine In Glimcher PW, Fehr E, Camerer C, & Poldrack RA (Eds), Neuroeconomics: decision making and the brain (pp. 367–385). New York: Academic Press.

Barnard ND, Noble EP, Ritchie T, Cohen J, Jenkins DJA, Turner-McGrievy G, … Ferdowsian H (2009). D2 dopamine receptor Taq1A polymorphism, body weight, and dietary intake in type 2 diabetes. Nutrition, 25(1), 58–65. [PubMed: 18834717]

Batterink L, Yokum S, & Stice E (2010). Body mass correlates inversely with inhibitory control in response to food among adolescent girls: An fMRI study. Neuroimage, 52, 1696–1703. [PubMed: 20510377]

Bello NT, Lucas LR, & Hajnal A (2002). Repeated sucrose access influences dopamine D2 receptor density in the striatum. Neuroreport, 13, 1575–1578. [PubMed: 12218708]

Berger B, Gaspar P, & Verney C (1991). Dopaminergic innervation of the cerebral cortex: Unexpected differences between rodant and primate. Trends in Neuroscience, 14, 21–27.

Berridge KC, Ho CY, Richard JM, & DiFeliceantonio AG (2010). The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. Brain Research, 1350, 43–64. [PubMed: 20388498]

Boomhower SR, & Rasmussen EB (2014). Haloperidol and rimonabant increase delay discounting in rats fed high-fat and standard-chow diets. Behavioral Pharmology, 25, 705–716.

Braet C, & Crombez G (2003). Cognitive interference due to food cues in childhood obesity. Journal of Clinical Child and Adolescent Psychology, 32, 32–39. [PubMed: 12573930]

Brooks SJ, Cedernaes J, & Schiöth HB (2013). Increased prefrontal and parahippo-campal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: a meta-analysis of fMRI studies. PLoS One, 8, e60393. [PubMed: 23593210]

Bruce AS, Holsen LM, Chambers RJ, Martin LE, Brooks WM, Zarcone JR, . . . Savage CR (2010). Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. International Journal of Obesity, 34, 1494–1500. [PubMed: 20440296]

Burger KS (2017). Frontostriatal and behavioral adaptations to daily sugar-sweetened beverage intake: a randomized controlled trial. The American Journal of Clinical Nutrition, 105(3), 555–563. [PubMed: 28179221]

Burger KS, & Berner LA (2014). A functional neuroimaging review of obesity, appetitive hormones and ingestive behavior. Physiology & Behavior 136, 121–127. [PubMed: 24769220]

Burger KS, & Stice E (2013). Elevated energy intake is correlated with hyperresponsivity in attentional, gustatory, and reward brain regions while anticipating palatable food receipt. American Journal of Clinical Nutrition, 97, 1188–1194. [PubMed: 23595877]

Burger KS, & Stice E (2012). Frequent ice cream consumption is associated with reduced striatal response to receipt of an ice cream-based milkshake. American Journal of Clinical Nutrition, 95(4), 810–817. [PubMed: 22338036]

Burger KS, & Stice E (2014). Greater striatopallidal adaptive coding during cue-reward learning and food reward habituation predict future weight gain. Neuroimage, 99, 122–128. [PubMed: 24893320]

Calitri R, Pothos EM, Tapper K Brunstrom JM, Rogers PJ (2010). Cognitive biases to healthy and unhealthy food words predict change in BMI. Obesity, 18, 2282–2287. [PubMed: 20379149]

Castellanos EH, Charboneau E, Dietrich MS, Park S, Bradley BP, Mogg K, & Cowan RL (2009). Obese adults have visual attention bias for food cue images: evidence for altered reward system function. International Journal of Obesity, 33, 1063–1073. [PubMed: 19621020]

Chouinard-Decorte F, Felsted J, & Small DM (2010). Increased amygdala response and decreased influence of internal state on amygdala response to food in overweight compared to healthy weight individuals. Appetite, 54, 639.

Colasanti A, Searle G, Long C, Hill S, Reiley R, Quelch D et al., (2012). Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. Biological Psychiatry, 72, 371–377. [PubMed: 22386378]

Cornier MA, Salzberg AK, Endly DC Bessesen DH, Tregellas JR (2010). Sex-based differences in the behavioral and neuronal responses to food. Physiology & Behavior, 99, 5538–5543.

Cornier MA, Melanson EL, Salzberg AK, Bechtell JL, Tregellas JR (2012). The effects of exercise on the neuronal response to food cues. Physiology & Behavior, 105, 1028–1034. [PubMed: 22155218]

Davis C & Claridge G (1998). The eating disorders as addiction: A psychobiological perspective. Addictive Behaviors, 23, 463–475. [PubMed: 9698975]

Davis C, Strachan S, & Berkson M (2004). Sensitivity to reward: Implications for overeating and overweight. Appetite, 42, 131–138. [PubMed: 15010176]

Davis JF, Tracy AL, Schurdak JD, Tschop MH, Lipton JW, Clegg DJ, & Benoit SC (2008). Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. Behavioral Neuroscience, 122, 1257–1263. [PubMed: 19045945]

Deckerbach T, Das S, Urban L, Salinardi T, Batra P, Robman A, . . . Roberts SB (2014). Pilot randomized trial demonstrating reversal of obesity-related abnormalities in reward system responsivity to food cues with a behavioral intervention. Nutrition and Diabetes, 4, e129. [PubMed: 25177910]

Demos KE, Heatherton TF, & Kelley WM (2012). Individual differences in nucleus accumbens activity to food and sexual images predict weight gain and sexual behavior. Journal of Neuroscience, 32, 5549–5552. [PubMed: 22514316]

Diamond A, Barnett W, Thomas J, & Munro S (2007). Preschool program improves cognitive control. Science, 318, 1387–1388. [PubMed: 18048670]

Diergaarde L, Pattij T, Nawijn L, Schoffelmeer AN, & Vries TJ (2009). Trait impulsivity predicts escalation of sucrose seeking and hypersensitivity to sucrose-associated stimuli. Behavioral Neuroscience, 123, 794–803. [PubMed: 19634937]

Dimitropoulos A, Tkach J, Ho A, & Kennedy J (2012). Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults. Appetite, 58, 303–312. [PubMed: 22063094]

Duckworth A, Tsukayama E, & Geier A (2010). Self-controlled children stay leaner in the transition to adolescence. Appetite, 54, 304–308. [PubMed: 20004223]

Due D, Huettel S, Hall W, Rubin D (2002). Activation in mesolimbic and visuospatial neural circuits elicited by smoking cues: Evidence from functional magnetic resonance imaging. American Journal of Psychiatry 159, 954–960. [PubMed: 12042183]

Eiden L, & Weihe E (2011). VMAT2: a dynamic regulator of brain monoaminergic neuronal function interacting with drugs of abuse. Annals of New York Academy of Science, 1216, 86–98.

Eichenbaum H, Cahill L, Gluck M, Hasselmo M, Keil F, Martin A, et al. (1999). Learning and memory: Systems analysis In Zigmond M, Bloom F, Landis S, Roberts J, & Squire L (eds). Fundamental Neuroscience (pp. 1455–1486). Academic Press: San Diego.

Ernst M, Luckenbaugh D, Moolchan E, Leff M, Allen R, Eshel N, London ED, Kimes A (2006) Behavioral predictors of substance use initiation in adolescent with and without attentiondeficit/ hyperactivity disorder. Pediatrics 117: 2030–2039. [PubMed: 16740845]

Evans G, Ruller-Rowell R, & Doan S (2012). Childhood cumulative risk and obesity: The mediating role of self-regulatory ability. Pediatrics, 129, e68. [PubMed: 22144695]

Ferreira J, Tellez L, Ren X, Yeckel C, & da Araujo I (2012). Regulation of fat intake in the absence of flavour signaling. Journal of Physiology, 590, 953–972. [PubMed: 22219333]

Figlewicz DP, Szot P, Chavez M, Woods SC, & Veith RC (1994). Intraventricular insulin increases dopamine transporter mRNA in rat VTA/substantia nigra. Brain Research, 644(2), 331–334. [PubMed: 8050044]

Francis L & Susman EJ (2009). Self-regulation failure and rapid weight gain in children from age 3 to 12 years. Archives of Disease in Children and Adolescents, 163, 297–302.

Frank GK, Reynolds JR, Shott ME, Jappe L, Yang TT, Tregellas JR, & O'Reilly RC (2012). Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacology, 307, 2031–2046.

Frank S, Laharnar N, Kullmann S, Veit R, Canova C, Hegner Y, et al., (2010). Processing of food pictures: Influence of hunger, gender, and calorie content. Brain Research, 1350, 159–166. [PubMed: 20423700]

Frankort A, Roefs A, Siep N, Roebroeck A, Havermans R, & Jansen A (2011). Reward activity in satiated overweight women is decreased during unbiased viewing but increased when imaging taste: An event-related fMRI study. International Journal of Obesity, 36, 1–11. [PubMed: 22041985]

Frohlich Z (1994). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. Nature 372, 315–341.

García-García I et al. Alterations of the salience network in obesity: a resting-state fMRI study. (2013). Hum. Brain Mapp. (34**),** 2786–2797. [PubMed: 22522963]

Geha PY, Aschenbrenner K, Felsted J, O'Malley SS, & Small DM (2013). Altered hypothalamic response to food in smokers. American Journal of Clinical Nutrition, 97, 15–22. [PubMed: 23235196]

Geha P, Cecchi G, Todd Constable R, Abdallah C & Small DM (2016). Reorganization of brain connectivity in obesity. Hum. Brain Mapp 38(3), 1403–1420. [PubMed: 27859973]

Geiger BM, Haburcak M, Avena NM, Moyer MC, Hoebel BG, & Pothos EN (2009). Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. Neuroscience, 159, 1193–1199. [PubMed: 19409204]

Graham R, Hoover A, Ceballos NA, & Komogortsev O (2011). Body mass index moderates gaze orienting biases and pupil diameter to high and low calorie food images. Appetite, 56, 577–586. [PubMed: 21291928]

Green E, Jacobson A, Haase L, & Murphy C (2011). Reduced nucleus accumbens and caudate nucleus activation to a pleasant taste is associated with obesity in older adults. Brain Research, 1386, 109–117. [PubMed: 21362414]

Gupta N, & Aron A (2011). Urges for food and money spill over into motor system excitability before action is taken. European Journal of Neuroscience, 33, 183–188. [PubMed: 21091805]

Hagelberg N, Kajander J, Nagren K, Hinkka S, Hietala J, & Scheinin H (2002). Mu-receptor agonism with alfentanil increases striatal dopamine D2 receptor binding in man. Synapse, 45, 279–287.

Hajnal A, Smith G, & Norgren R (2004). Oral sucrose stimulation increases accumbens dopamine in the rat. American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 286, R31–R37.

Haltia L, Rinne J, Merisaari H, Maguire R, Savontaus E, Helin S, Nagren K, & Kaasinen V (2007). Effects of intravenous glucose on dopaminergic function in the human brain in vivo. Synapse, 61, 748–756. [PubMed: 17568412]

Harris RB (1990). Role of set-point theory in regulation of body weight. The FASEB Journal, 4, 3310–3318. [PubMed: 2253845]

Hardman C, Herbert V, Brunstrom J, Munafo M, & Rogers P (2014). Dopamine and food reward: Effects of acute tyrosine/phenylalanine depletion on appetite. Physiology and Behavior, 105, 1202–1207.

Hetherington MM, Bell Al., Rolls BJ (2000). Effects of repeat consumption on pleasantness, preference, and intake. British Food Journal, 102, 507–521.

Hetherington MM, Pirie LM, & Nabb S (2002). Stimulus satiation: effects of repeated exposure to foods on pleasantness and intake. Appetite, 38, 19–28. [PubMed: 11883914]

Holsen L, Savage C, Martin L, Bruce A, Lepping R, Ko E, Brooks W . ., Goldstein JM (2012). Importance of reward and prefrontal circuitry in hunger and satiety: Prader-Willi syndrome vs simple obesity. International Journal of Obesity, 36, 638–647. [PubMed: 22024642]

Houben K (2011). Overcoming the urge to splurge: Influencing eating behavior by manipulating inhibitory control. Journal of Behavior Therapy and Experimental Psychiatry, 42, 384–388. [PubMed: 21450264]

Houben K & Jansen A (2011). Training inhibitory control. A recipe for resisting sweet temptations. Appetite, 56, 345–349. [PubMed: 21185896]

Huerta CI, Sarkar PR, Duong TQ, Laird AR, & Fox PT (2014). Neural bases of food perception: coordinate-based meta-analyses of neuroimaging studies in multiple modalities. Obesity (Silver Spring), 22, 1439–1446. [PubMed: 24174404]

Ivezaj V, Stoeckel L, Avena N, Benoit S, Conason A, Davis J, Gearhardt A, Goldman R, Mitchell J, Ochner C, Saules K, Steffen K, Stice E, & Sogg S (2017). Obesity and addiction: can a complication of surgery help us understand the connection? Obesity Reviews, 18, 765–775. [PubMed: 28429582]

Jalabert M, Bourdy R, Coutin J, Veinante P, Manzoni O, Barrot M et al., (2011). Neuronal circuits underlying acute morphine action on dopamine neurons. Proceedings of the National Academy of Science, USA, 108, 16445–16450.

Jastreboff AM, Sinha R, Lacadie C, Small DM, Sherwin RS, & Potenza MN (2013). Neural correlates of stress- and food cue-induced food craving in obesity: association with insulin levels. Diabetes Care, 36, 394–402. [PubMed: 23069840]

Jonsson B, Bjorvell H, Levander S & Rossner S (1986). Personality traits predicting weight loss outcome in obese patients. Acta Psychiatrica Scandinavica, 74, 384–387. [PubMed: 3811999]

Johnson PM, & Kenny PJ (2010). Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nature Neuroscience, 13, 635–641. [PubMed: 20348917]

Kakoschke N, Kemps E, & Tiggemann M (2014). Attentional bias modification encourages healthy eating. Eating Behaviors, 15, 120–124. [PubMed: 24411764]

Kelley AE, Will MJ, Steininger TL, Zhang M, & Haber SN (2003). Restricted daily consumption of a highly palatable food (chocolate Ensure(R)) alters striatal enkephalin gene expression. European Journal of Neuroscience, 18, 2592–2598. [PubMed: 14622160]

Kemps E, Tiggemann M, & Hollitt S (2014a). Biased attentional processing of food cues and modification in obese individuals. Health Psychology, 93, 1391–1401.

Kemps E, Tiggemann M, Orr J, & Grear J (2014b). Attentional retraining can reduce chocolate consumption. Journal of Experimental Psychology: Applied, 20, 94–102. [PubMed: 24079387]

Kishinevsky F, Cox J, Murdaugh D, Stoeckel L, Cook E, & Weller R (2012). fMRI reactivity on a delay discounting task predicts weight gain in obese women. Appetite, 58, 582–592. [PubMed: 22166676]

Kirsch P, Reuter M, Mier D, Lonsdorf T, Stark R, Gallhofer B, … Hennig J (2006). Imaging gene-substance interactions: The effect of the DRD2 TaqIA polymorphism and the dopamine agonist bromocriptine on the brain activation during the anticipation of reward. Neuroscience Letters, 405(3), 196–201. [PubMed: 16901644]

Klonoff DC (2009). The personalized medicine for diabetes meeting summary report. Journal of Diabetes Science and Technology, 3(4), 677–679. [PubMed: 20144312]

Krakowski M, Czobor P, & Citrome L (2009). Weight gain, metabolic parameters, and the impact of race in aggressive inpatients randomized to double-blind clozapine, olanzapine or haloperidol. Schizophrenia Research, 110, 95–102. [PubMed: 19269139]

Krank M, Stewart SH, O'Connor R, Woicik PB, Wall AM, Conrold PJ (2011) Structural, concurrent, and predictive validity of the Substance Use Risk Profile Scale in early adolescence. Addict Behav 36: 37–46. [PubMed: 20826056]

Kringelbach ML, O'Doherty J, Rolls ET, & Andrews C (2003). Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cerebral Cortex, 13, 1064–1071. [PubMed: 12967923]

Kroemer NB, & Small DM (2016). Fuel not fun: Reinterpreting attenuated brain responses to reward in obesity. Physiology & Behavior, 162, 37–45. [PubMed: 27085908]

Laviolette S, Nader K, van der Kooy D (2002). Motivational state determines the functional role of the mesolimbic dopamine system in the mediation of opiate reward processes. Behavior and Brain Research, 129, 17–19.

Lawrence NS, Hinton EC, Parkinson JA, & Lawrence AD (2012). Nucleus accumbens response to food cues predicts subsequent snack consumption in women and increased body mass index in those with reduced self-control. Neuroimage, 63, 415–422. [PubMed: 22776461]

Lawrence N, Verbruggen F, Morrison S, Parslow D, O'Sullivan J, Javaid M, et al. (2014) Training response inhibition to food to reduce overeating. J Psychopharmacology 28 (supplement): A130.

Leeuwen A, Creemers H, Verhulst F, Ormel J, Huizink A (2011) Are adolescents gambling with cannabis use? A longitudinal study of impulsivity measures and adolescent substance use: The TRAILS study. J Stud Alcohol Drugs 72: 70–78. [PubMed: 21138713]

Leidy H, Lepping R, Savage C, Harris C, 2011 Neural responses to visual food stimuli after a normal vs. higher protein breakfast in breakfast-skipping teens: a pilot fMRI study. Obesity 19, 2019–2025. [PubMed: 21546927]

Liang N, Hajnal A, & Norgren R (2006). Sham feeding corn oil increases accumbens dopamine in the rat. American Journal of - Regulatory, Integrative and Comparative Physiology, 291, R1236–1239.

Lips MA, Wijngaarden MA, van der Grond J, van Buchem MA, de Groot GH, Rombouts SA, ... & Veer IM (2014). Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. The American journal of clinical nutrition, 100, 524–531. [PubMed: 24965310]

Loseth G, Ellingsen D, & Leknes S (2014). State-dependent μ-opioid modulation of social motivation. Frontiers in Behavioral Neuroscience, 8, 1–15. [PubMed: 24478648]

Loxton N, & Dawe S (2006). Reward and punishment sensitivity in dysfunctional eating and hazardous drinking women: Association with family risk. Appetite, 47, 361–371. [PubMed: 16846665]

Luo S, Liang Y, & Cincotta H (1999). Intracerebroventricular administration of bromocriptine ameliorates the insulin-resistant/glucose-intolerant state in hamsters. Neuroendocrinology, 69(3), 160–166. [PubMed: 10087448]

Luo S, Meier AH, & Cincotta AH (1998). Bromocriptine reduces obesity, glucose intolerance and extracellular monoamine metabolite levels in the ventromedial hypothalamus of Syrian hamsters. Neuroendocrinology, 68(1), 1–10. [PubMed: 9695933]

Mackintosh N (1974). The Psychobiology of animal learning. Academic Press; London.

Malmberg M, Kleinjan M, Vermulst A, Overbeek G, Monshouwer K, Lammers J, Engels R (2012) Do substance use risk personality dimensions predict the onset of substance use in early adolescence? A variable- and person-centered approach. J Youth Adolesc 41: 1512–1525. [PubMed: 22623315]

Martin LE, Holsen LM, Chambers RJ, Bruce AS, Brooks WM, Zarcone JR, . . . Savage CR (2010). Neural mechanisms associated with food motivation in obese and healthy weight adults. Obesity, 18, 254–260. [PubMed: 19629052]

McGue M, Lacono W, Legrand L, Malone S, Elkins I (2001) Origins and consequences of age at first drink: Associations with substance-use disorders, disinhibitory behavior, and psychopathology, and P3 amplitude. Alcohol Clin Exp Res 25: 1156–1165. [PubMed: 11505047]

Mehta S, Melhorn S, Smeraglio A, Tyagi V, Grabowski T, Schwartz M et al., (2012). Regional brain response to visual food cues is a marker of satiety that predicts food choice. American Journal of Clinical Nutrition, 96, 989–999. [PubMed: 22990034]

Meltzer H (2002). Mechanism of action of atypical antipsychotric drugs (pp. 819–831). In Davis K, Coyle J, & Nemeroff C (eds.). Neuropsychopharmacology: The Fifth Generation of Progress. American College of Neuropscyhopharmacology.

Mick I, Myers J, Stokes P, Erritzoe D, Colasanti A, Bowden-Jones H et al. (2014). Amphetamine induced endogenous opioid release in the human brain detected with [11C]carfentanil PET: Replication in an independent cohort. International Journal of Neuropsychopharmacology, 1–6. [PubMed: 23953038]

Miller G (2011). The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. Journal of Neurochemistry, 116, 164–176. [PubMed: 21073468]

Miller R (2009). Mechanisms of action of antipsychotic drugs of different classes, refractoriness to therapeutic effects of classical neuroleptics, and individual variation in sensitivity to their actions. Current Neuropharmacology, 7, 302–314. [PubMed: 20514210]

Mirenowicz J, & Schultz W (1994). Importance of unpredictability for reward responses in primate dopamine neurons. Journal of Neurophysiology, 72, 1255–1263.

Murdaugh D, Cox J, Cook E, & Weller R (2012). fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. Neuroimage, 59, 2709–2721. [PubMed: 22332246]

Murray E, Brouwer S, McCutcheon R, Harmer CJ, Cowen PJ, & McCabe C (2014). Opposing neural effects of naltrexone on food reward and aversion: Implications for the treatment of obesity. Psychopharmacology, 231, 4323–4335. doi:10.1007/s00213-014-3573-7. [PubMed: 24763910]

Murdaugh D, Cox J, Cook E, & Weller R (2012). fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. Neuroimage, 59, 2709–2721. [PubMed: 22332246]

Murray S, Tulloch A, Gold MS, & Avena NM (2014b). Hormonal and neural mechanisms of food reward, eating behaviour and obesity. Nat Rev Endocrinol, 10(9), 540–552. [PubMed: 24958311]

Myrick H, Anton R, Li X, Henderson S, Drobes D, Voronin K, George M (2004). Differential Brain Activity in Alcoholics and Social Drinkers to Alcohol Cues: Relationship to Craving. Neuropsychopharmacology 29, 393–402. [PubMed: 14679386]

Nederkoorn C, Braet C, Van Eijs Y, Tanghe A, & Jansen A (2006). Why obese children cannot resist food: The role of impulsivity. Eating Behaviors, 7, 315–322. [PubMed: 17056407]

Nederkoorn C, Jansen E, Mulkens S & Jansen A (2007). Impulsivity predicts treatment outcome in obese children. Behaviour Research and Therapy, 45, 1071–1075. [PubMed: 16828053]

Nijs IM, Franken IH, & Muris P (2010a). Food-related Stroop interference in obese and normal-weight individuals: behavioral and electrophysiological indices. Eating Behaviors, 11, 258–265. [PubMed: 20850061]

Nijs IM, Muris P, Euser AS, & Franken IH (2010b). Differences in attention to food and food intake between overweight/obese and normal-weight females under conditions of hunger and satiety. Appetite, 54, 243–254. [PubMed: 19922752]

Nikolova YS, Ferrell RE, Manuck SB, & Hariri AR (2011). Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. Neuropsychopharmacology, 36, 1940–1947. [PubMed: 21593733]

Noble EP, Blum K, Ritchie T, Montgomery A, & Sheridan PJ (1991). Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism or gene ism. Archives of General Psychiatry, 48(7), 648. [PubMed: 2069496]

Nolan-Poupart S, Veldhuizen MG, Geha P, Small DM (2013). Midbrain response to milkshake correlates with ad libitum milkshake intake in the absence of hunger. Appetite, 60, 168–74. [PubMed: 23064394]

Norman A, Pulido C, Squeglia L, Spadoni A, Paulus M (2011) Neural activation during inhibition predicts initiation of substance use in adolescence. Drug Alcohol Depend 119: 216–223. [PubMed: 21782354]

O'Doherty JP, Deichmann R, Critchley HD, & Dolan RJ (2002). Neural responses during anticipation of a primary taste reward. Neuron, 33, 815–826. [PubMed: 11879657]

Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM, & Tataranni PA (2006). Brain abnormalities in human obesity: a voxel-based morphometric study. Neuroimage, 31, 1419–25. [PubMed: 16545583]

Phillips PEM, Stuber GD, Heien MLAV, Wightman RM, & Carelli RM (2003). Subsecond dopamine release promotes cocaine seeking. Nature, 422(6932), 614–618. [PubMed: 12687000]

Plotnikoff R, Costigan S, Williams R, Hutchesson M, Kennedy S, Robards S, et al., (2015). Effectiveness of interventions targeting physical activity, nutrition, and healthy weight for university and college students: A systematic review and meta-analysis. International Journal of Behavioral Nutrition and Physical Activity, 12, 45. [PubMed: 25890337]

Pollard H, Llorens-Cortes C, & Schwartz J (1977). Enkephalin receptors on dopaminergic neurons in rat striatum. Nature, 268, 745–747. [PubMed: 197427]

Ranaldi R, Pocock D, Zereik R, & Wise A (1999). Dopamine fluctuations in the nucleus accumbens during maintenance, extinction, and reinstatement of intravenous damphetamine self-administration. Journal of Neuroscience, 19, 4102–4109. [PubMed: 10234038]

Ren X, Ferreira J, Zhous L, Shammah-Lagnado S, Yeckel C, & de Araujo I (2010). Nutrient selection in the absence of taste receptor signaling. Journal of Neuroscience, 30, 8012–8023. [PubMed: 20534849]

Robbins T, & Everitt B (1999). Motivation and reward (pp. 1245–1260). In Zigmond M, Bloom F, Landis S, Roberts J, & Squire L (eds). Fundamental Neuroscience. San Diego, Academic Press.

Robertson SH, Boomhower SR, & Rasmussen EB (2017). High-fat diet alters weight, caloric intake, and haloperidol sensitivity in the context of effort-based responding. Behavioral Pharmacology, 28, 323–333.

Robertson SH, & Rasmussen EB (2017). Effects of a cafeteria diet on delay discounting in adolescent and adult rats: Alterations on dopaminergic sensitivity. Journal of Psychopharmacology, 31, 1419–1429. [PubMed: 29067887]

Robinson TE, & Berridge KC (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Research Review, 18, 247–291.

Rosenbaum M, Sy M, Pavlovich K, Leibel RL, & Hirsch J (2008). Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. Journal of Clinical Investigation, 118, 2583–2591. [PubMed: 18568078]

Sadler JR, Shearrer GE, & Burger KS (2018). Body mass variability is represented by distinct functional connectivity patterns. NeuroImage, 181, 55–63. [PubMed: 29966718]

Salbe AD, DelParigi A, Pratley RE, Drewnowski A, & Tataranni PA (2004). Taste preferences and body weight changes in an obesity-prone population. American Journal of Clinical Nutrition, 79, 372–378. [PubMed: 14985209]

Schlam TR, Wilson NL, Shoda Y, Mischel W, & Ayduk O (2013). Preschoolers' delay of gratification predicts their body mass 30 years later. Journal of Pediatrics, 162, 90–93. [PubMed: 22906511]

Schultz W, Dayan P, & Montague PR (1997). A neural substrate of prediction and reward. Science, 275, 1593–1599. [PubMed: 9054347]

Schultz W (1998). Predictive reward signal of dopamine neurons. Journal of Neurophysiology, 80(1), 1–27. [PubMed: 9658025]

Seeyave D, Coleman S, Appugliese D, Corwyn R, Bradley R, Davidson N, . . . Lumen JC (2009). Ability to delay gratification at age 4 years and risk of overweight at age 11 years. Archives of Pediatric and Adolescent Medicine, 163, 303–308.

Sevgi M, Rigoux L, Kuhn AB, Mauer J, Schilbach L, Hess ME, … Tittgemeyer M (2015). An Obesity-Predisposing Variant of the FTO Gene Regulates D2R-Dependent Reward Learning. Journal of Neuroscience, 35(36), 12584–12592. [PubMed: 26354923]

Shearrer G, Stice E, & Burger K (2018). Adolescents at high-risk for obesity show greater striatal response to increased sugar content of milkshakes. American Journal of Clinical Nutrition 107, 859–866. [PubMed: 29771283]

Shao R, Read J, Behrens T, & Rogers R (2013). Shifts in reinforcement signalling while playing slot-machines as a function of prior expereicne and impulsivity. Translational Psychiatry, 3, e213. [PubMed: 23321810]

Small DM, Jones-Gotman M, & Dagher A (2003). Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. Neuroimage, 19, 1709–1715. [PubMed: 12948725]

Small DM, Veldhuizen MG, Felsted J, Mak YE, &, McGlone F (2008). Separable substrates for anticipatory and consummatory food chemosensation. Neuron, 57, 786–797. [PubMed: 18341997]

Small DM, Zatorre RJ, Dagher A, Evans AC, & Jones-Gotman M (2001). Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain, 124, 1720–1733. [PubMed: 11522575]

Sotak B, Hnasko T, Robinson S, Kremer E, & Palmiter R (2005). Dysregulation of dopamine signaling in the dorsal striatum inhibits feeding. Brain Research, 1061, 88–96. [PubMed: 16226228]

Steele KE, Prokopowicz GP,Schweitzer MA, Magunsuon TH, Lidor AO, Kuwabawa H, . . . Wong DF (2010). Alterations of central dopamine receptors before and after gastric bypass surgery. Obesity Surgery, 20, 369–374. [PubMed: 19902317]

Stice E, Burger KS, & Yokum S (2013). Relative ability of fat and sugar tastes to activate reward, gustatory, and somatosensory regions. American Journal of Clinical Nutrition, 98, 1377–1384. [PubMed: 24132980]

Stice E, Burger K, & Yokum S (2015). Reward region responsivity predicts future weight gain and moderating effects of the *TaqIA* allele. Journal of Neuroscience, 35, 10316–10324. [PubMed: 26180206]

Stice E, Figlewicz DP, Gosnell BA, Levine AS, & Pratt WE (2013). The contribution of brain reward circuits to the obesity epidemic. Neuroscience & Biobehavioral Reviews, 37, 2047–2058. [PubMed: 23237885]

Stice E, Lawrence N, Kemps E, & Veling H (2016). Training motor responses to food: A novel treatment for obesity targeting implicit processes. Clinical Psychology Review, 49, 16–27. [PubMed: 27498406]

Stice E, Shaw H, & Marti CN (2006). A meta-analytic review of obesity prevention programs for children and adolescents: the skinny on interventions that work. Psychological Bulletin, 132, 667–691. [PubMed: 16910747]

Stice E, Spoor S, Bohon C, & Small DM (2008a). Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. Science, 322, 449–452. [PubMed: 18927395]

Stice E, Spoor S, Bohon C, Veldhuizen MG, & Small DM (2008b). Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. Journal of Abnormal Psychology, 117, 924–935. [PubMed: 19025237]

Stice E, & Yokum S (2014). Brain reward region responsivity of adolescents with and without parental substance use disorder. Psychology of Addictive Behaviors, 28, 805–815. [PubMed: 24128289]

Stice E, & Yokum S (2016). Gain in body fat associated with increased striatal response to palatable food cues whereas body fat stability is associated with decreased striatal response. Journal of Neuroscience, 36, 6949–6956. [PubMed: 27358453]

Stice E, & Yokum S (2018). Relation of neural response to palatable food tastes and images to future weight gain: Using bootstrap sampling to examine replicability of neuroimaging findings. NeuroImage, 183, 522–531. [PubMed: 30144570]

Stice E, Yokum S, Blum K, & Bohon C (2010a). Weight gain is associated with reduced striatal response to palatable food. Journal of Neuroscience, 30, 13105–13109. [PubMed: 20881128]

Stice E, Yokum S, Bohon C, Marti N, & Smolen A (2010b). Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. Neuroimage, 50, 1618–1625. [PubMed: 20116437]

Stice E, Yokum S, & Burger K (2013). Elevated reward region responsivity predicts future substance use onset but not overweight/obesity onset. Biological Psychiatry, 73, 869–876. [PubMed: 23312561]

Stice E, Yokum S, Burger KS, Epstein L, & Smolen A (2012). Multilocus genetic composite reflecting dopamine signaling capacity predicts reward circuitry responsivity. Journal of Neuroscience, 32, 10093–10100. [PubMed: 22815523]

Stice E, Yokum S, Burger KS, Epstein LH, & Small DM (2011). Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. Journal of Neuroscience, 31, 4360–4366. [PubMed: 21430137]

Stice E, Yokum S, Veling H, Kemps E, & Lawrence N (2017). Pilot test of a novel food response and attention training treatment for obesity: Brain imaging data suggest actions shape valuation. Behaviour Research and Therapy, 94, 60–70. [PubMed: 28505470]

Stuber G, Klanker M, Bowers M, Joosten R, Feenstra M, & Bonci A (2008). Reward-predictive cues enhance excitatory synaptic strength onto midbrain dopamine neurons. Science, 321, 1690–1692. [PubMed: 18802002]

Sun X, Kroemer N, Veldhuizen M, Babbs A, de Araujo I, Gitelman D et al., (2005). Basolateral amygdala response to food cues in the absence of hunger is associated with weight gain susceptibility. Journal of Neuroscience, 35, 7964–7976.

Sutin A, Ferrucci L, Zonderman A, & Terracciano A (2011). Personality and obesity across the adult life span. Journal of Personality and Social Psychology, 101, 579–592. [PubMed: 21744974]

Tang DW, Fellows LK, Small DM, & Dagher A (2012). Food and drug cues activate similar brain regions: A meta-analysis of functional MRI studies. Physiology & Behavior, 106, 317–324. [PubMed: 22450260]

Tapert S, Cheung E, Brown G, Frank L, Paulus M, Schweinsburg A, Meloy M, Brown S (2003). Neural response to alcohol stimuli in adolescents with alcohol use disorder. Archives of General Psychiatry 60, 727–735. [PubMed: 12860777]

Tellez L, Medina S, Han W, Ferreira J, Licona-Limon P, Ren X, . . . de Araujo IE (2013). A gut lipid messenger links excess dietary fat to dopamine deficiency. Science, 341, 800–802. [PubMed: 23950538]

Thanos PK, Michaelides M, Piyis YK, Wang GJ, & Volkow ND (2008). Food restriction markedly increases dopamine D2 receptor (D2R) in a rat model of obesity as assessed with in-vivo muPET imaging ([11C] raclopride) and in-vitro ([3H] spiperone) autoradiography. Synapse, 62, 50–61. [PubMed: 17960763]

Thompson J, Drysdale M, Baimel C, Kaur M, MacGowan T, Pitman K et al., (2017). Obesity-induced structural and neuronal plasticity in the lateral orbitofrontal cortex. Neuropsychopharmacology, 42, 1480–1490. [PubMed: 28042870]

Tindell AJ, Berridge KC, & Aldridge JW (2004). Ventral pallidal representation of pavlovian cues and reward: population and rate codes. Journal of Neuroscience, 24, 1058–1069. [PubMed: 14762124]

Tobler PN, Fiorillo CD, & Schultz W (2005). Adaptive coding of reward value by dopamine neurons. Science, 307, 1642–1645. [PubMed: 15761155]

Tryon MS, Carter CS, DeCant R, & Laugero KD (2013). Chronic stress exposure may affect the brain's response to high calorie food cues and predispose to obesogenic eating habits. Physiology & Behavior, 120233–242. doi:10.1016/j.physbeh.2013.08.010.

Tuominen L, Tuulari J, Karlsson H, Hirvonen J, Helin S, Salminen P et al. (2015). Aberrant mesolimbic dopamine-opiate interaction in obesity. NeuroImage, 122, 80–86. [PubMed: 26260431]

Umhau J, Petrulis S, Diaz R, Rawlings R, & George D (2003). Blood glucose is correlated with cerebrospinal fluid neurotransmitter metabolites. Neuroendocrinology, 78, 339–343. [PubMed: 14688447]

Val-Laillet D, Layec S, Guerin S, Meurice P, & Malbert CH (2011). Changes in brain activity after a diet-induced obesity. Obesity (Silver Spring), 19, 749–756. [PubMed: 21212769]

Van Meer F, van der Laan LN, Adan RAH, Viergever MA, & Smeets PAM (2015). What you see is what you eat: An ALE meta-analysis of the neural correlates of food viewing in children and adolescents. Neuroimage, 104, 35–43. [PubMed: 25285373]

Veling H, Koningsbruggen G, Aarts H, & Stroebe W (2014). Targeting impulsive processes of eating behavior via the Internet. Effects on body weight. Appetite, 78C, 102–109.

Volkow N, Wang G, Fowler J, Logan J, Gatley S, Hitzemann R et al., (1997). Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subects. Nature, 386, 830–833. [PubMed: 9126741]

Volkow N, Wang G, Telang F, Fowler J, Logan J, Hayne M et al., (2007). Profound decreases in dopamine release in striatum in detoxified alcoholics: Possible orbitofrontal involvement. J of Neuroscience, 27, 12700–12706.

Vucetic Z, Carlin JL, Totoki K, et al., (2012). Epigenetic dysregulation of the dopamine system in diet-induced obesity. Journal of Neurochemistry, 120, 891–898. [PubMed: 22220805]

Wang GJ, Volkow ND, & Fowler JS (2002). The role of dopamine in motivation for food in humans: implications for obesity. Expert Opinion on Therapeutic Targets, 6, 601–609. [PubMed: 12387683]

Wang GJ, Volkow ND, Logan J, Pappas N Wong C, Zhu W et al. (2001). Brain dopamine and obesity. Lancet, 357, 354–357. [PubMed: 11210998]

Werthmann J, Field M, Roefs A, Nederkoorn C, & Jansen A (2014). Attentional bias for chocolate increase chocolate consumption: An attention bias modification study. Journal of Behavior Therapy and Experimental Psychiatry, 45, 136–143. [PubMed: 24140811]

Weygandt M, Mai K, Dommes E, Leupelt V, Hackmack K, Kahnt T, . . . Haynes J-D (2013). The role of neural impulse control mechanisms for dietary success in obesity. Neuroimage, 83, 669–678. [PubMed: 23867558]

Weygandt M, Mai K, Dommes E, Ritter K, Leupelt V, Spranger J, & Haynes J (2015). Impulse control in the dorsolateral prefrontal cortex counteracts post-diet weight regain in obesity. Neuroimage, 109318–327. doi:10.1016/j.neuroimage.2014.12.073.

Winter S, Yokum S, Stice E, Osipowicz K, & Lowe M (2017). Elevated reward response to receipt of palatable food predicts future weight variability in healthy-weight adolescents. American Journal of Clinical Nutrition, 105, 781–789. [PubMed: 28228422]

Wise R & Rompre P (1989). Brain dopamine and reward. Annual Review of Psychology, 40, 191–225.

Wise RA, Newton P, Leeb K, Burnette B, Justice JB (1995). Fluctuations in nucleus accumbens dopamine concentrations during intravenous cocaine self-administration in rats. Psychopharmacology, 120, 10–20. [PubMed: 7480530]

Wiskerke J, Schetters D, van Es I, van Mourik Y, Hollander B, Schoffeimeer A, & Pattij T (2011). Mu-opioid receptors in the nucleus accumbens shell region mediate the effects of amphetamine on inhibitory control but not impulsive choice. Journal of Neuroscience, 31, 262–272. [PubMed: 21209211]

World Health Organization. Obesity and overweight. Fact Sheet 311 Retrieved 11.10.2014 from http://amro.who.int/common/Display.asp?Lang=E&RecID=10203. 2013

Yokum S, Gearhardt A, Harris J, Brownell K, & Stice E (2014). Individual differences in striatum activity to food commercials predicts weight gain in adolescence. Obesity (Silver Spring), 22, 2544–2551. [PubMed: 25155745]

Yokum S, Marti CN, Smolen A, & Stice E (2015). Relation of the multilocus genetic composite reflecting high dopamine signaling capacity to future increases in BMI, Appetite, 87, 38–45. [PubMed: 25523644]

Yokum S, Ng J, & Stice E (2011). Attentional bias for food images associated with elevated weight and future weight gain: An fMRI study. International Journal of Obesity, 19, 1775–1783.

Yokum S, Ng J, & Stice E (2012). Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. International Journal of Obesity, 36, 656–664. [PubMed: 21894161]

Zellner M, & Ranaldi R (2010). How conditioned stimuli acquire the ability to activate VTA dopamine cells: A proposed neurobiological component of reward-related learning. Neuroscience and Biobehavioral Reviews, 34, 769–780. [PubMed: 19914285]

Zhou & Palmiter (1995). Dopamine-deficient mice are severely hypoactive, adipsic, and aphagic. Cell, 83, 1197–1209. [PubMed: 8548806]

Highlights:

- Youth at risk for weight gain show greater reward region response to food tastes.
- Elevated brain reward region response to food cues predicts future weight gain.
- A genetic propensity for greater dopamine signaling predicts weight gain.
- Youth who show greater food reward-cue learning show greater weight gain.
- Overeating reduces reward region response to high-calorie foods.
- Data provide strong support for the incentive sensitization theory of obesity.

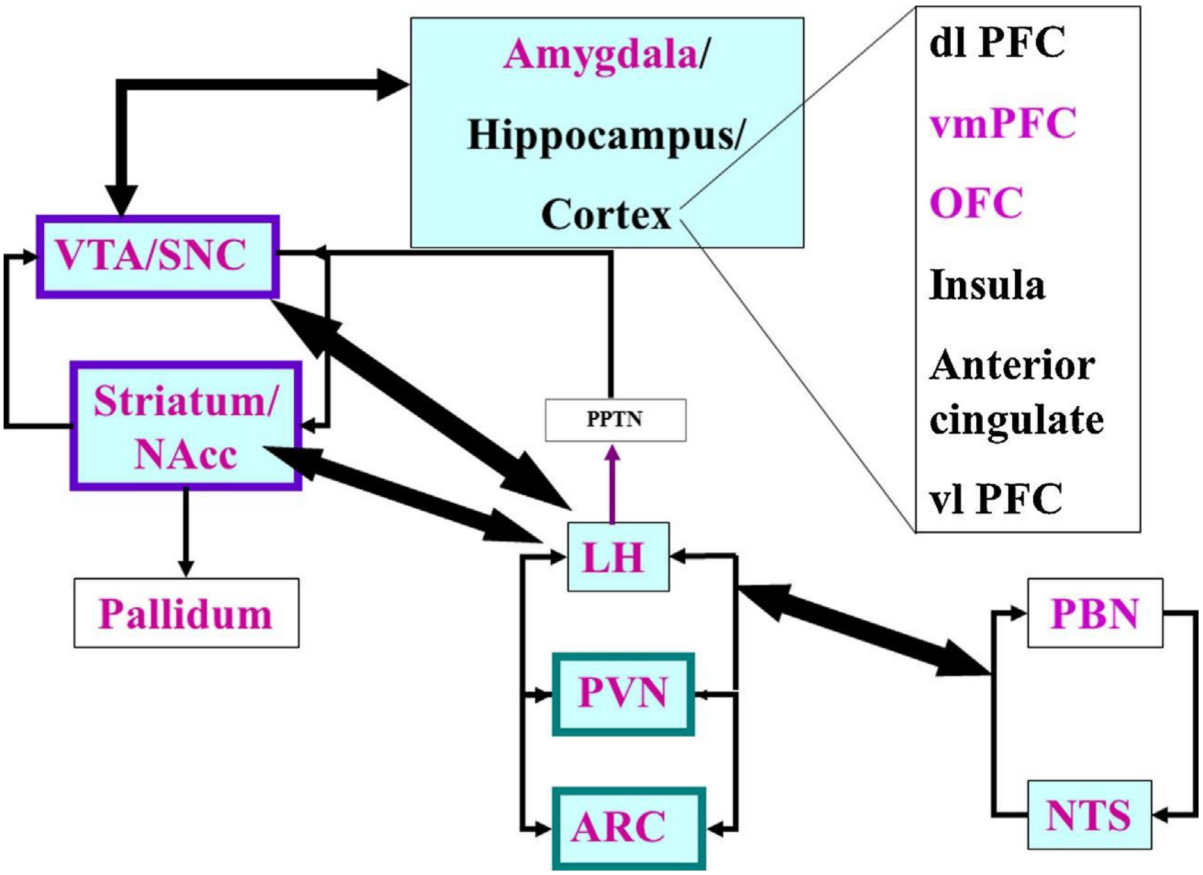

Figure 1.

Integrative signaling of homeostatic and hedonic feeding in the CNS. Major monosynaptic connections are shown, emphasizing the extensive anatomical interconnectivity of functional sets of circuitry that mediate aspects of feeding. Teal-framed boxes represent medial hypothalamic sites (PVN, ARC) that had historically been considered key sites for energy homeostasis, coordinating the regulation of body weight, metabolism, and short- and long-term feeding. Purple-framed boxes represent the central dopaminergic cell bodies (VTA/SNC) and mesolimbic projections (striatum/NAcc), historically considered the major regulatory sites of motivated behaviors. The dopaminergic circuitry is connected with hypothalamic circuitry as well as limbic circuitry (amygdala/hippocampus/cortical areas). All regions shaded in pale blue represent CNS sites that are direct receptive targets of the endocrine signals of caloric abundance (insulin, leptin) and caloric need (ghrelin). These include brainstem (PBN/NTS: key relay nuclei for sensory and motor aspects of feeding); hypothalamic, dopaminergic, and limbic regions. Brain regions highlighted with magenta labelling are direct target regions for mu opioid stimulation of feeding. Cortex areas are a major focus of current animal and clinical studies and contributing sub-regions differ between rodents and humans; however the OFC and subareas of the PFC are implicated for both.

ARC, arcuate nucleus; PVN, paraventricular nucleus of the hypothalamus; LH, lateral hypothalamic area; NAcc, nucleus accumbens; VTA, ventral tegmental area; SNC, substantia nigra pars compacta; NTS, nucleus of the tractus solitarius; PBN, parabrachial

nucleus; dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; PPTN, pedunculopontine tegmental nucleus; OFC, orbitofrontal cortex.

Reproduced with permission from Stice et al., 2013.

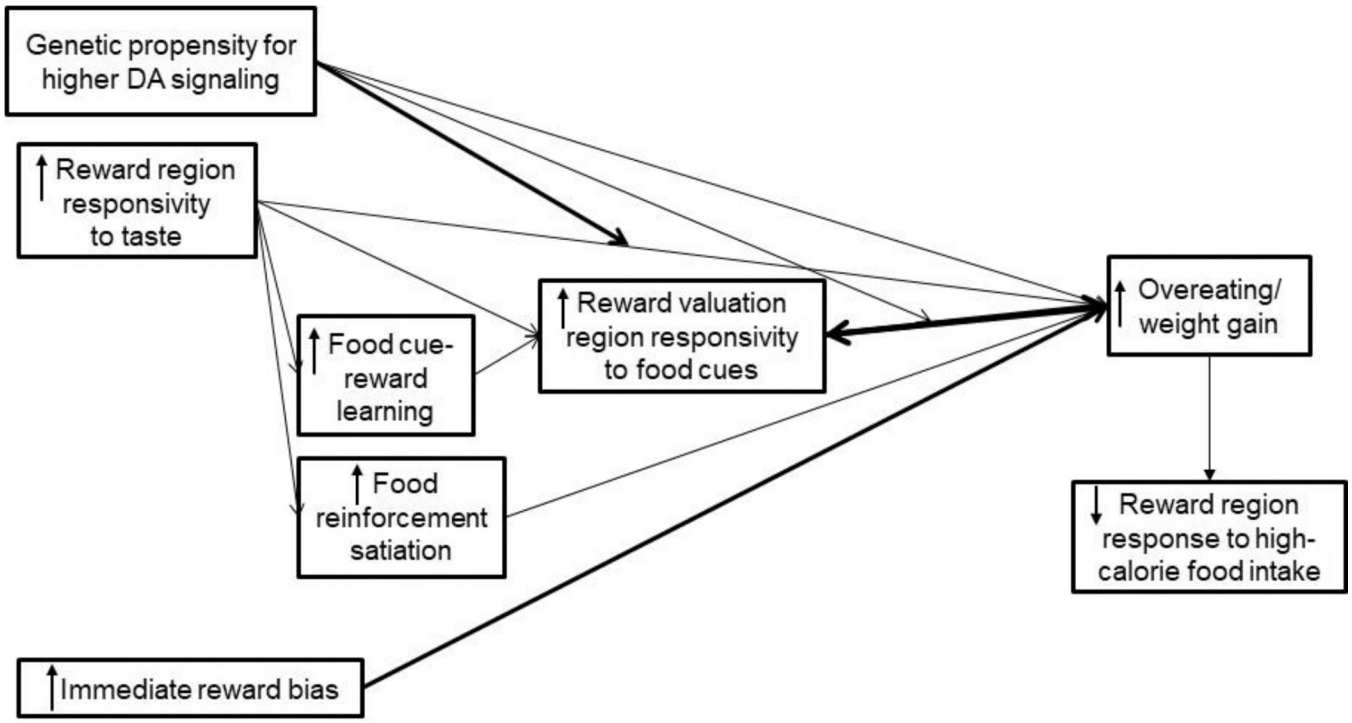

Figure 2.
Presentation of a refined version of the Dynamic Vulnerability Model of Obesity

Table 1.

An abridged summary of fMRI studies investigating features of the multiple brain-based theories of weight gain and obesity.

Study	Design summary; sampling frame	Followup (mo.)	Findings	Theory: support +; no support −
Randomized Controlled Experiments				
Burger 2017	Participants were randomized to daily consumption of one of two branded, sugar sweetened beverages over a three-week period. were scanned before and after the intervention; Data were analyzed using whole brain analysis; 20 participants	3 weeks	Daily beverage consumption resulted in decreases in dorsal striatal response during receipt of the consumed beverage (r = −0.46), and decreased ventromedial prefrontal response during logo-elicited anticipation of the consumed beverage (r = −0.44). This decrease in prefrontal response correlated with increases in behavioral disinhibition toward the logo of the consumed beverage (r = 0.54; P = 0.02). Daily beverage consumption also increased precuneus response to both juice logos when compared to a tasteless control (r = 0.45).	Incentive sensitization: + Reward deficit: + Inhibitory control deficit: +
Cornier et al., 2012	Participants were scanned before and after completing a 24-week exercise intervention (no control group); Data were analyzed using whole-brain analyses; 12 participants	6	Change in insula BOLD activity in response to positively hedonic food vs nonfood objects from pre- to post intervention positively correlated with changes in fat mass (r = .78) and body weight (r = .76).	Incentive sensitization: +
Deckersbach et al., 2014	Participants were randomized to a 6month weight-loss intervention vs control group; Data were analyzed using regions-ofinterest analysis; 13 participants	6	Participants in the weight loss intervention compared to those in the control group showed increases in putamen BOLD activity in response to low-calorie food images vs high-calorie food images (r = .71) and attenuation in putamen BOLD activity in response to high-calorie food vs lowcalorie food images (r = −. 54).	Incentive sensitization: +
Murdaugh et al., 2012	Participants scanned before and after completing a 12-week weight loss intervention; Data were analyzed using both regionsof-interest and whole-brain analyses; 25 participants	9	Greater BOLD activity in nucleus accumbens (r = .61) and insula (r = .68) in response to high-calorie food images vs car images at baseline predicted increases in BMI.	Incentive sensitization: +
Weygandt et al., 2013	Participants were scanned before completing a 12week weight loss intervention; Data were analyzed using regions-ofinterest analysis; 16 participants	3	Subjects with limited food delay gratification lost less weight over follow-up (r = −.42). BOLD activity in the ventromedial prefrontal cortex (r = .86) and dorsolateral prefrontal cortex (r = .82 and r = .85) in response to subjective value of delayed meals positively correlated with weight loss. Activation in the anterior insula (r = −.82 and r = −.85) in response to subjective value of delayed meals negatively correlated with weight loss. BOLD activity in a region of the dorsomedial prefrontal cortex in response to subjective value of delayed meals positively correlated with weight loss (r = .87) and BOLD activity in another region was negative correlated with weight loss (r = −.87).	Inhibitory control deficit: +
Repeated Measure Studies				

Study	Design summary; sampling frame	Followup (mo.)	Findings	Theory: support +; no support −
Stice et al., 2010a	Data were analyzed using regions-ofinterest analysis; 26 females	6	Females who gained weight showed a reduction in caudate response to palatable food receipt vs tasteless solution relative to weight-stable women.	Reward deficit: −
Prospective Studies				
Batterink et al., 2010	Data were analyzed using regions-ofinterest analysis; 35 females	12	No significant correlations between regions implicated in inhibitory control and change in BMI.	Inhibitory control deficit: −
Burger & Stice, 2014	Data were analyzed using regions-ofinterest analysis; 35 females	24	Greater increase in ventral pallidum BOLD activity to palatable food receipt vs tasteless solution receipt over repeated exposures was associated with future increases in BMI (r = . 39). Greater decrease in caudate BOLD activity to food receipt vs tasteless solution receipt over repeated exposures was associated with future increases in BMI (r = −.69).	Incentive sensitization: + Reward deficit: −
Chouinard Decorte et al., 2010	Data were analyzed using regions-ofinterest analysis; 26 participants	12	Greater BOLD activity in the amygdala to palatable food aromas vs odorless predicted future increases in BMI (effect sizes not reported).	Incentive sensitization: + Reward deficit: −
Demos et al., 2012	Data were analyzed using both regionsof-interest and whole-brain analyses; 48 females	6	Greater BOLD activity in the nucleus accumbens to food images predicted future increases in BMI (r = .37).	Incentive sensitization: + Reward deficit: −
Geha et al., 2013	Data were analyzed using whole-brain analyses; 15 participants	12	BOLD activity in the midbrain, hypothalamus, anterior thalamus, ventral pallidum, and nucleus accumbens to palatable food receipt vs tasteless solution receipt correlated positively with change in BMI (M r = 0.83).	Reward surfeit: + Reward deficit: −
Kishinevsky et al., 2012	Data were analyzed using both regions-of-interest and whole-brain analyses; 17 females	25	Lower BOLD activity in the inferior frontal gyrus (r = −.78), middle frontal gyrus ($M r$ = −. 79), and inferior parietal lobe (r = −.74) on hard vs easy trials in a monetary delay discounting task was associated with greater increases in BMI.	Inhibitory control deficit: +
Stice et al., 2008a	Data were analyzed using regions-ofinterest analysis; 33 females	12	No significant main effects of BOLD activity in the putamen (r = .19) and caudate (r = .26) to palatable food receipt vs tasteless solution receipt on BMI change. Interactions between *TaqIA* and BOLD response in the putamen (r = .45) and caudate (r = .42) to palatable food receipt vs tasteless solution receipt were correlated with change in BMI: less activation in these regions was associated with greater BMI increase in subjects with the *TaqIA* A1 allele and greater activation in these regions was associated with greater BMI increase in those without the *TaqIA* A1 allele.	Reward surfeit: + Reward deficit: +
Stice et al., 2010b	Data were analyzed using both regionsof-interest and whole-brain analyses; 39 females	12	There were no significant main effects of BOLD activity on increases in BMI over follow-up. Interactions between *TaqIA* and BOLD response in the putamen (r = 0.33) and orbitofrontal cortex (r = 0.60) in response to palatable food images vs unpalatable food images were correlated with change in BMI: less activation in these regions was associated with greater BMI increase in subjects with the *TaqIA* A1 allele and greater activation in these regions was associated with greater BMI increase in those without the *TaqIA* A1 allele.	Incentive sensitization: + Reward deficit: +
Stice et al., 2015	Data were analyzed using both regionsof-	36	Greater BOLD activity in the orbitofrontal cortex to anticipated palatable food receipt vs	Reward surfeit: + Incentive sensitization: +

Study	Design summary; sampling frame	Followup (mo.)	Findings	Theory: support +; no support −
	interest and whole-brain analyses; 153 participants		anticipated tasteless solution receipt predicted future increases in body fat (r = .32). Interaction between *TaqIA* and BOLD response in caudate to palatable food receipt vs tasteless solution receipt was correlated with change in body fat (r = 0.24): less activation in these regions was associated with greater BMI increase in subjects with the *TaqIA* A1 allele and greater activation in these regions was associated with greater BMI increase in those without the *TaqIA* A1 allele.	Reward deficit: +
Sun et al., 2015	Data were analyzed using both regionsof-interest and whole-brain analyses; 32 participants	12	No significant main effects of BOLD activity in reward regions in response to palatable food receipt vs tasteless solution receipt and to palatable food cue vs tasteless solution cue on BMI change. Interaction between *TaqIA* and BOLD response in amygdala to palatable food receipt vs tasteless solution receipt correlated with change in BMI: less activation in this region was associated with greater BMI increase in subjects with the *TaqIA* A1 allele (r = −.69) and greater activation in this region was related to greater BMI increase in subjects without the A1 allele (r = .68).	Reward surfeit: + Incentive sensitization: − Reward deficit: +
Yokum et al., 2011	Data were analyzed using regions-ofinterest analysis; 35 females	12	Greater BOLD orbitofrontal cortex response to cues signaling the impending presentation of palatable food images predicted future increases in BMI (r = .42).	Incentive sensitization: + Reward deficit: −
Yokum et al., 2014	Data were analyzed using regions-ofinterest analysis; 30 participants;	12	Greater BOLD caudate response to food commercials - nonfood commercials (r = .57) and to food commercials - television show (r = .51) predicted future increases in BMI.	Incentive sensitization: + Reward deficit: −
Cross-sectional of obesity risk status				
Shearrer, Stice, & Burger	Group study define by obesity risk status; Data were analyzed using both regionsof-interest and whole-brain analyses; 108 participants	n.a.	High-risk (n=53) vs. low-risk (n=54) adolescents showed greater BOLD response to milkshake > tasteless solution receipt in the primary gustatory and oral somatosensory cortices ($M r$ = .37). High-risk adolescents also showed greater caudate, gustatory and oral somatosensory response to specifically a high-sugar milkshake > tasteless solution contrast (r = .35).	Reward surfeit: +
Stice et al. 2011	Group study define by obesity risk status; Data were analyzed using both regionsof-interest and whole-brain analyses; 60 participants	n.a.	Healthy weight adolescents at high (n = 35) versus low risk (n =25) for future weight gain based on parental obesity status showed greater activation in caudate ($M r$ = .41) in response to palatable food receipt vs tasteless solution receipt and greater activation in caudate (r = .42), putamen (M r = .46), and orbitofrontal cortex (r = .72) in response to winning money display vs neutral coin display.	Reward surfeit: + Reward deficit: −