Chapter 6
Neural Vulnerability Factors that Increase Risk for Weight Gain: Prevention and Treatment Implications

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Introduction

Nearly 70% of US adults are overweight or obese [1], which increases risk for coronary heart disease, atherosclerotic cerebrovascular disease, colorectal cancer, and all-cause mortality, is credited with 300,000 US deaths and $ 150 billion in health-related expenses yearly [2, 3]. Unfortunately, treatments almost never result in lasting weight loss and virtually all obesity prevention programs have not reduced future obesity onset [4, 5]. An improved understanding of the risk processes that give rise to weight gain should guide the design of more effective preventive programs and treatments. At present, most risk factors that predict future weight gain show only weak effects [6–9]. For example, the predictive effects for parental obesity, a well replicated risk factor for future weight gain, have only ranged from an $r = 0.18$ to 0.21 in large epidemiologic studies [e.g., 7, 9].

Theorists have focused on the role of reward circuitry in obesity because eating palatable food increases activation in regions implicated in reward, including the striatum, midbrain, amygdala, and orbitofrontal cortex (OFC) [10–12] and causes dopamine (DA) release in the dorsal striatum, with the amount released correlating with meal pleasantness ratings [13]. Indeed, even delivery of high-fat food directly to the gut, bypassing the oral cavity, has been shown to induce robust striatal dopamine release in rodents [14]. It has been posited that aberrant reward-related responses to food intake and/or cues override homeostatic processes of hunger and fullness, resulting in excess adipose tissue and weight gain [e.g., 15]. Further, data indicate that appetitive hormones thought to influence homeostatic determinants of food intake (e.g., leptin, peptide YY, glucagon-like peptide 1) act by altering reward value of food [16]. In support of hedonically driven food intake, direct phar-

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macological activation of the striatum prompts hyperphagia in animals, increasing preferential intake of high-fat/sugar foods, even in sated animals [17]. Agonist and antagonist experiments suggest that DA signaling plays a larger role in reward learning and that opioid peptide signaling plays a larger role in hedonic pleasure from food intake [18], though reward regions contain both DA and opioid receptors and opioid agonists cause DA signaling [19], implying the two neurotransmitter systems are tightly intertwined.

Reward Surfeit and Incentive Sensitization Theories of Obesity

The reward surfeit model holds that individuals who showed greater responsivity of reward regions to food intake, which is presumably inborn, are at elevated risk for overeating and consequent weight gain [20]. The incentive sensitization model posits that repeated intake of palatable foods results in an elevated responsivity of reward valuation regions to cues that are repeatedly associated with palatable food intake via conditioning, which prompts elevated food intake when these cues are encountered [18].

Consistent with these theories, obese versus lean humans show greater responsivity of brain regions associated with reward and motivation (striatum, amygdala, OFC) to pictures of high-fat/sugar foods versus low-fat/sugar foods and control images [21–28] and to pictorial cues that signal impending palatable food receipt [20, 29]. These data are supported by studies examining acute and longer-term food intake. Specifically, midbrain and medial OFC activity in response to milkshake receipt positively predicted subsequent *ad libitum* milkshake consumption and BOLD response in the ventral striatum during exposure to food images positively predicts later snack consumption [30, 31]. Using objectively measured energy intake over a two-week period in lean adolescents, a positive relation was observed between energy intake beyond basal metabolic needs and BOLD response during cues predicting food receipt in regions thought to encode visual processing and attention (visual and anterior cingulate cortices), salience (precuneus), as well as the primary gustatory cortex (frontal operculum) and (reward/motivation) striatum [32]. Animal experiments indicate that firing of striatal and ventral pallidum DA neurons initially occurs in response to receipt of a novel palatable food, but that after repeated pairings of palatable food intake and cues that signal impending receipt of that food, DA neurons begin to fire in response to reward-predictive cues and no longer fire in response to food receipt [33–35]. Theorists posit this shift during cue-reward learning acts to either update knowledge regarding the predictive cues or attribute reward value to the cues themselves thereby guiding behavior [36–39].

Critically, fMRI studies indicate that hyper-responsivity of reward regions (striatum, amygdala, OFC) to palatable food images [40, 41], palatable food odors [42] or cues that signal impending presentation of palatable food images [43] predicts future weight gain. Additionally, teens that exhibit greater striatal response to high-fat/sugar food commercials show elevated weight gain over 1-year

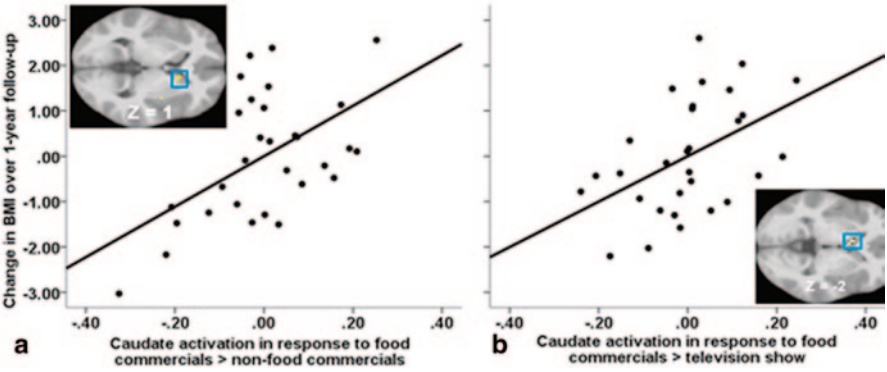

Fig. 6.1 Partial regression plots showing the relations of **a** activation in the caudate (MNI coordinates: 12, 14, 1) in response to food commercials > non-food commercials and **b** activation in the caudate (MNI coordinates: −9, 14, −2) in response to food commercials > television show to change in BMI over 1-year follow-up

follow-up (r = 0.47–0.51; Fig. 6.1; [44]). Elevated amygdala, midbrain, thalamus, hypothalamus, ventral pallidum, and nucleus accumbens responsivity to tastes of milkshake have also predicted weight gain over 1-year follow-up [42, 45].

Interestingly, there is evidence that the effects of hyper-responsivity of reward regions to food and food cues shows significantly stronger relations to future weight gain for individuals with a genetic propensity for greater DA signaling capacity in reward regions. Adolescents with elevated caudate and putamen responsivity to milkshake tastes who have a genetic propensity for greater DA signaling due to possessing an A2/A2 *TaqIA* allele showed significantly greater weight gain over 1-year follow-up [46]. Likewise, teens who show elevated striatal/OFC response to palatable food images and who had a genetic propensity for greater DA signaling due to possessing an A2/A2 *TaqIA* allele, also showed elevated future weight gain [27]. Similar effects have emerged for another genotype (no seven-repeat or longer alleles of the *DRD4* gene [*DRD4*-S]) that has been associated with elevated DA signaling [27]. Data from a large ($N = 155$) ongoing study revealed that lean teens who showed greater OFC response to a cue that signals impending milkshake receipt were more likely to gain weight over 2-year follow-up ($r = 0.29$) and that this relation was significantly stronger for youth with a genetic propensity for greater DA signaling capacity in reward circuitry as indexed by a multilocus composite that reflects the number of alleles associated with elevated DA signaling (Fig. 6.2). We examined this multilocus score because it relates more strongly to reward region responsivity than the individual alleles used to calculate this composite genetic risk score [47, 48]. Theoretically, this is because a greater number of these genotypes, regardless of the particular combination, are associated with greater DA signaling capacity. The multilocus composite was scored as follows: *TaqIA* A1/A1, *DRD2-141*C Ins/Ins, *DRD4*-L, *DAT1* 10R/10R, and *COMT* Met/Met genotypes were assigned a score of 0 ('low'); *TaqIA* A2/A2, *DRD2-141*C Ins/Del and Del/Del, *DRD4*-S, *DAT1* 9R, and *COMT* Val/Val genotypes were assigned a score of 1 ('high'), and

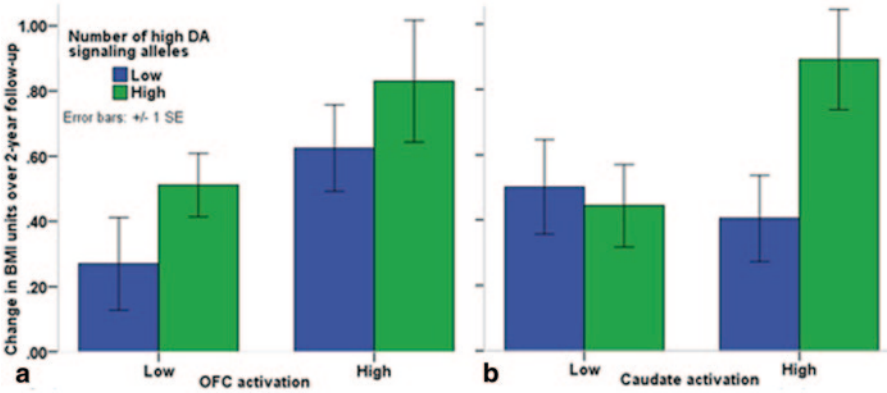

Fig. 6.2 Change in BMI predicted by the interaction between the number of high DA signaling alleles and **a** OFC activation and **b** caudate activation in response to anticipatory milkshake receipt

TaqIA A1/A2 and *COMT* Met/Val genotypes received a score of 0.5. Scores were summed to create the composite. Humans with the A2/A2 allele versus an A1 allele of the *Taq1A* polymorphism and the Del allele versus Ins/Ins genotype of the *DRD2-141*C Ins/Del polymorphism show more D2 receptors [49]. Humans with the shorter than seven alleles (*DRD4*-S) versus seven-repeat or longer allele (*DRD4*-L) of the *DRD4* genotype show greater *in vitro* DA functioning and stronger response to DA agonists [50, 51]. Humans with the nine-repeat allele (*DAT1-S)* versus homozygous for the ten-repeat allele (*DAT1*-L) of the *DAT1* show lower *DAT1* expression [52], theoretically increasing synaptic DA clearance, producing lower basal DA levels and increased phasic DA release [53]. Val homozygotes versus Met homozygotes of the *Catechol-O-methyltransferase* (*COMT* val^{158}met) gene putatively have lower basal striatal DA levels and greater phasic DA release [54]. Individuals with higher multilocus scores showed greater future weight gain in three separate studies (Fig. 6.3; [55]), confirming that this effect is replicable.

Thus, studies from multiple independent labs have found that individuals who show elevated reward region responsivity to palatable food intake are more likely to enter a prolonged period of positive energy balance and gain weight, providing key behavioral data in support of the reward surfeit theory of obesity. Studies from multiple independent labs have also found that individuals who show elevated reward region responsivity to cues that have been associated with palatable food intake show elevated future weight gain, providing behavioral support for the incentive sensitization theory of obesity. There was also evidence that the predictive relations of elevated reward region responsivity to palatable food intake and food cues to future weight gain are stronger for individuals with a genetic propensity for greater DA signaling capacity in reward regions, which might be construed as further support for the reward surfeit model. These results imply that reducing habitual intake of high-fat and high-sugar foods should theoretically reduce the conditioning process that leads to elevated reward region responsivity to food cues, which may be an

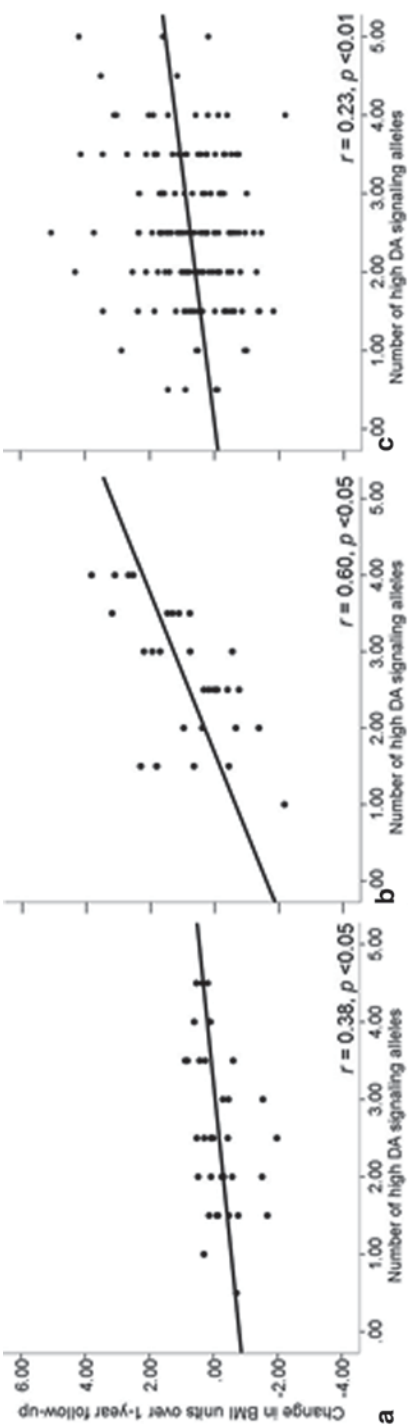

Fig. 6.3 Partial regression plots showing the effects of the number of high DA signaling alleles (multilocus composite score) on change in BMI over 1-year follow-up in **a** 38 young females (*M* age = 20.9 ± 1.2; *M* BMI = 28.1; BMI range = 24.0–39.0), **b** 30 adolescents (56.7% female; *M* age = 15.2 ± 1.0; *M* BMI = 26.9; BMI range = 19.5–37.9), and **c** 161 adolescents (50.6% female; *M* age = 15.2 ± 1.0; *M* BMI = 20.8; BMI range = 17.0–26.1), while controlling for baseline BMI

effective method of reducing risk for weight gain. However, the fact that behavioral weight loss programs typically result in reduced intake of such foods, typically leading to a 10 % weight loss on average, but do not produced sustained weight loss implies that it is very difficult to reduce reward region hyper-responsivity to food cues once it has emerged.

Reward Deficit Theory of Obesity

The reward deficit model of obesity posits that individuals with lower sensitivity of DA-based reward regions overeat to compensate for this deficiency [56]. Apparently consistent with this theory, obese versus lean adults show lower striatal DA D2 receptor availability [57–59], though two other studies found no significant group differences [60, 61], which might have been due to the smaller samples sizes in the latter studies. Obese versus lean adults show lower capacity of nigrostriatal neurons to synthesize DA [62], and less striatal responsivity to tastes of high-fat/sugar beverages [20, 46, 63–65]. Obese versus lean rats likewise have lower basal DA levels and D2 receptor availability and less ex vivo DA release in response to electrical stimulation in nucleus accumbens and dorsal striatum tissue [66–69]. Interestingly, a recent study in humans [58] found a positive correlation between BMI and DA release in the dorsal striatum and substantia nigra in response to amphetamine, suggesting that D2 receptor availability may not be closely coupled with degree of DA response from rewarding experiences.

Although the above cross-sectional findings appear to provide some support for the reward deficit theory of obesity, prospective and experimental findings indicate that overeating contributes to reward region hypo-responsivity. 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, rather than hypo-responsivity [70]. Young women who gained weight over a 6-month period showed a reduction in striatal responsivity to palatable food receipt relative to women who remained weight stable [71]. This finding converges with experimental overfeeding studies involving animals; rats randomized to overeating conditions that results in weight gain versus control conditions show down-regulation of post-synaptic D2 receptors, and reduced D2 sensitivity, extracellular DA levels in the nucleus accumbens and DA turnover, and lower sensitivity of DA reward circuitry to food intake, electrical stimulation, amphetamine administration, and potassium administration [69, 72–76]. Of note, rats that had consumed a high-fat/sugar diet continued to eat that food when subsequently paired with foot shocks, whereas chow-diet rats would not eat high-fat/sugar food when paired with foot shocks [76], suggesting that energy dense diets may induce compulsive eating. Further, pigs randomized to a weight gain intervention versus a stable weight condition showed reduced resting activity in the midbrain and nucleus accumbens [77]. The reduced DA signaling capacity appears to occur because habitual intake of high-fat diets causes decreased synthesis of oleoylethanolamine, a gastrointestinal lipid messenger [14]. Further, people who report elevated intake of particular foods show reduced striatal response during intake of that food, independent of BMI [78–80].

Given that animals that habitually use drugs of abuse that produce similar down-regulation of reward regions will work to keep DA levels in the nucleus accumbens above a certain level [81–83], Geiger and associated [74] speculate that rats which have experienced diet-induced down-regulation of DA circuitry may similarly overeat to increase DA signaling. However, a more recent study found that mice in which reduced striatal DA signaling from food intake was experimentally induced through intragastric feeding of high-fat food worked less for intragastric administration of high-fat food and consumed less food *ad lib* than control mice [14]. These experimental results seem incompatible with the notion that an induced down-regulation of DA reward circuitry leads to compensatory overeating. Results from the Tellez et al. [14] study also provided further evidence that intake of high-fat food can result in reduced DA response to food intake, independent of weight gain per se.

Interestingly, the relations between lower striatal response to milkshake receipt and weight gain over 1-year follow-up [20] and between lower putamen and OFC response to palatable food images and weight gain over 1-year follow-up [27] were significantly stronger for youth with the A1 allele, which is associated with less DA signaling, implying that any reduction in DA signaling caused by overeating may have a more pronounced reward deficit effect for those at genetic risk for lower DA signaling. Similar effects have emerged for individuals with the seven-repeat allele of the *DRD4* gene, which is also associated with reduced DA signaling capacity [27].

Thus, studies have provided little prospective or experimental support for the reward deficit theory of obesity. Specifically, no prospective study has reported a main effect between reduced reward region responsivity to food intake or cues and future weight gain. Indeed, as noted, prospective studies have found that greater responsivity of reward circuitry, including the amygdala, midbrain, ventral pallidum, nucleus accumbens, and striatal, rather than reduced responsivity, to palatable milkshake intake predicts future weight gain [e.g., 42, 45]. And recent data found that inducing down-regulation of DA response to food intake resulted in less caloric intake and motivation for food than observed in control mice [14]. Thus, findings collectively suggest that the reduced DA signaling capacity of reward circuitry can be acquired from overeating, but provide little support for the notion that this contributes to overeating and subsequent weight gain.

Translating Findings from Brain Imaging Research into an Obesity Prevention Program

Thus, emerging research suggests that obese versus lean individuals show elevated reward region responsivity to images of high-fat/high-sugar foods and that this increases risk for future weight gain. Fortunately, there is evidence that prefrontal regions can reduce reward region responsivity to appetitive cues [84]. Cognitive reappraisals, such as thinking of the long-term health consequences of eating unhealthy food when viewing images of such foods, increases inhibitory region (dlPFC, vlPFC, vmPFC, lateral OFC, superior and inferior frontal gyrus) activation and

decreases reward region (ventral striatum, amygdala, ACC, VTA, posterior insula) and attention region (precuneus, posterior cingulate cortex) activation relative to contrast conditions, such as imagined intake [85–88]. Stoeckel and associates [89] used real-time fMRI biofeedback to augment the effects of cognitive reappraisals in reducing reward region responsivity and increasing inhibitory region responsivity to images of palatable foods; the training resulted in significantly greater reduction in medial OFC, right ventral striatum, and right amygdala, as well as greater activation in an inhibitory control region (inferior frontal cortex [IFG]) in response to palatable food images. Thus, findings suggest that cognitive reappraisals may reduce hyper-responsivity of reward regions to food cues and increase inhibitory control region activation, which is crucial because our environment is replete with food images and cues (e.g., ads on TV) that contribute to overeating. For instance, US teens are exposed to over 5000 unhealthy food commercials yearly [90]. Indeed, exposure to unhealthy food commercials results in greater caloric intake of the advertised foods and other unhealthy foods [90–92]. Accordingly, we developed an obesity prevention program that trained participants to use cognitive reappraisals when confronted with unhealthy tempting foods. We hypothesize that if participants learn to automatically apply these cognitive reappraisals, they will show reduced reward and attention region responsivity and increased inhibitory region responsivity to food images and cues signaling impending delivery of a high-fat/high-sugar food, which should result in reduced caloric intake and weight gain.

Emerging data also suggests that obese versus lean individuals show reduced recruitment of reward regions during intake of high-fat/high-sugar foods, which is either inborn of acquired, with some evidence that this may increase risk for future weight gain. If overeating energy-dense food reduces reward region response to such food, which may prompt compensatory overeating to achieve the same satisfaction experienced previously, reducing fat and sugar intake may help people avoid this induced-reward deficit that may contribute to obesity. Such a "palate-retraining" intervention may also reduce preferences for high-fat/sugar foods, which may contribute to weight gain. Reducing intake of dietary fat decreases preferences and frequency of future consumption of previously preferred high-fat foods and increases acceptance of low-fat foods [93, 94], implying a relation between habitual fat intake and preferences for fat foods. Chronic intake of a high-fat diet theoretically leads to reduced oral sensitivity, prompting compensatory escalations in fat intake to experience same degree of reward [95]. We therefore included a palate-retraining component to our neuroimaging-informed obesity prevention program wherein participants reduce fat and sugar intake to decrease taste preferences for high-fat/sugar foods and avoid the reduced reward region responsivity to high-fat/sugar food intake observed in obese humans. We hypothesize that if intervention participants reduce overall consumption of fat and sugar, they will show an increase in striatal response to receipt of a high-fat/high-sugar milkshake, which may reduce risk for compensatory overeating.

We therefore evaluated an obesity prevention program that trained young adults to (a) use cognitive reappraisals when confronted with tempting palatable foods and (b) gradually reduce intake of fat and sugar in their diets to decrease risk for a

blunted striatal response to palatable food intake [96]. Young adults at risk for future weight gain by virtue of weight concerns ($N=148$) were randomized to this new *Minding Health* prevention program, an alternative prevention program promoting participant-driven gradual reductions in caloric intake and increases in physical activity (the *Healthy Weight* intervention), or an obesity education video control condition, completing assessments at pre, post, and 6-month follow-up. A subset of *Minding Health* and control participants completed an fMRI scan at pre and post assessing neural response to images of high-fat/sugar foods and to receipt and anticipated receipt of a high-fat/sugar food. *Minding Health* participants showed significantly greater reductions in body fat than controls and percentage of caloric intake from fat and sugar than *Healthy Weight* participants, though these effects attenuated somewhat by 6-month follow-up. However, *Healthy Weight* participants showed greater reductions in BMI and eating disorder symptoms than *Minding Health* participants. *Minding Health* participants showed greater activation of an inhibitory control region (IFG) and reduced activation of an attention/expectation region (mid cingulate gyrus) in response to palatable food images relative to pretest and controls. Although the *Minding Health* intervention produced some of the hypothesized effects, it only affected some outcomes and the effects often showed limited persistence.

Future Research Directions

This review highlights several important directions for future research. First, although a small number of prospective brain imaging studies have investigated neural vulnerability factors that predict future weight gain, the vast majority of the literature reviewed herein is cross-sectional. It will therefore be important for additional large sample prospective brain imaging studies to identify neural vulnerability factors that predict future weight gain. Second, it will be important to investigate environmental, social, and biological factors that amplify and mitigate the effects of these vulnerability factors on future weight gain. Third, it would be useful for additional prospective repeated-measures studies to attempt to capture the plasticity of reward region responsivity to food images/cues and food receipt, that appears to emerge secondary to overeating, which may play a role in maintaining overeating. If randomized experiments could be used to address these three directions for future research, much stronger inferences regarding these etiologic processes would be possible. Finally, we hope that future research will continue to try to translate findings from brain imaging studies into prevention and treatment interventions for obesity. For instance, we suspect it would be useful to test whether real-time fMRI biofeedback could be used to enhance the efficacy of the cognitive reappraisal-based obesity prevention program described above. It might likewise be possible to use non-invasive brain stimulation procedures to augment the efficacy of these types of obesity prevention programs.

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