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Neurogenetic and Neuroimaging Evidence for a Conceptual Model of Dopaminergic Contributions to Obesity

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Abstract

As the incidence of obesity continues to rise, clinicians and researchers alike are seeking explanations for why some people become obese while others do not. While caloric intake and physical activity most certainly play a role, some individuals continue to gain weight despite careful attention to these factors. Increasing evidence suggests that genetics may play a role, with one potential explanation being genetic variability in genes within the neurotransmitter dopamine pathway. This variability can lead to a disordered experience with the rewarding properties of food. This review of literature examines the extant knowledge about the relationship between obesity and the dopaminergic reward pathways in the brain, with particularly strong evidence provided from neuroimaging and neurogenetic data. Pubmed, Google Scholar, and Cumulative Index to Nursing and Allied Health Literature searches were conducted with the search terms

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dopamine, obesity, weight gain, food addiction, brain regions relevant to the mesocortical and mesolimbic (reward) pathways, and relevant dopaminergic genes and receptors. These terms returned over 200 articles. Other than a few sentinel articles, articles were published between 1993 and 2013. These data suggest a conceptual model for obesity that emphasizes dopaminergic genetic contributions as well as more traditional risk factors for obesity, such as demographics (age, race, and gender), physical activity, diet, and medications. A greater understanding of variables contributing to weight gain and obesity is imperative for effective clinical treatment.

Keywords

dopamine; obesity; BMI; genetics

As the incidence of obesity continues to rise, clinicians and researchers alike are seeking explanations for why some people become obese while others do not. Though this problem has been extensively studied, a large portion of the variation remains to be explained. While caloric intake and physical activity most certainly play a role, some individuals continue to gain weight despite careful attention to these factors. Increasing evidence suggests that genetics may play a role, with one potential explanation being variability in genes within the neurotransmitter dopamine pathway. Recent years have seen an explosion of literature examining the relationship of dopamine to obesity. This relationship has been confirmed by neurogenetic and neuroimaging data and demonstrates biological similarities to relationships seen with some types of addictions such as cocaine, alcohol, and gambling.

In this review of literature, we examine the extant knowledge about the relationship between obesity and the dopaminergic reward pathways in the brain, with particularly strong evidence provided from neuroimaging and neurogenetic data. We employed PubMed, Cumulative Index to Nursing and Allied Health Literature, and Google Scholar database searches for peer-reviewed reports of research in humans and animals published in English over the past 20 years, which is the approximate time period within which the neurogenetic and neuroimaging fields have come to prominence. We used the search terms *dopamine, obesity, weight gain, food addiction*, brain regions relevant to the mesocortical and mesolimbic (reward) pathways (i.e., *frontal cortex, nucleus accumbens, ventral tegmental area, and striatum*), and relevant dopaminergic genes and receptors, which are described subsequently. These terms returned over 200 articles. Other than a few sentinel articles, articles were published between 1993 and 2013. From these results, we suggest a conceptual model of obesity that takes into account dopaminergic genetic and environmental factors.

Background

The Problem of Obesity

According to the Centers for Disease Control, between 2007 and 2009, the incidence of obesity in America increased 1.1% (National Center for Health Statistics, 2010), netting an additional 2.4 million Americans who met the criterion for obesity (body mass index [BMI] of greater than 30 kg/m²). Obesity is a modifiable risk factor that has a strong correlation with various comorbidities, including cardiovascular disease and diabetes. Moreover,

obesity (associated with poor diet and lack of physical activity) is one of the leading causes of death in the United States (Mokdad, Marks, Stroup, & Gerberding, 2004). Cultural and social factors most certainly play a role in the development of obesity, but individual elements determine who will or will not become obese in a given situation.

Generally, weight gain leading to obesity is attributed to an intake of calories in excess of what is used in metabolism and physical activity. Traditional weight loss plans involve a reduction in the intake of food and an increase in the amount of calories expended in exercise. However, these diet plans are not successful for many people. In some cases, people experience a “yo-yo” effect, where they stay on the plan for a period of time and lose weight but then quickly regain it when they go off the plan, only to start the cycle over again. Some researchers have suggested that those who have extreme difficulty in long-term weight management may be genetically different from other individuals. While obesity is considered a polygenic disorder, some of these genetic differences may revolve around the reward neurotransmitter dopamine.

The Role of Dopamine

Researchers have long considered dopamine to be relevant to the study of obesity (Hoebel, 1985). Although many other neurotransmitters (such as gamma-aminobutyric acid, glutamine, serotonin, and norepinephrine) can play a role in food intake, experimental evidence indicates that dopamine is the one most often directly implicated in food reward. Olds and Milner’s classic experiments (1954) first showed that rats will obsessively press a lever to receive stimulation to the dopaminergic reward centers of their brains. These findings constituted the first suggestion that the release of dopamine in the brain is associated with pleasurable feelings.

The pleasant feelings associated with food intake are also associated with the release of dopamine (Baik, 2013). In individuals with normal functioning of their dopaminergic systems, even a brief cue, such as smell or sight, of a familiar food can begin the dopamine release process. Once the response to these cues begins, the dopaminergically normal person perceives the whole experience of eating as being pleasurable. In particular, highly palatable foods, such as those with higher sugar and fat content, stimulate the dopaminergic pathways more than less palatable foods (Baik, 2013).

The dopamine release also normally leads to a feeling of satiety after food is consumed, as demonstrated by Barry, Clarke, and Petry’s (2009) observation that if dopamine release is blocked chemically, subjects report an increase in appetite. This chemical block occurs clinically when patients are placed on antipsychotic medications, which are often associated with weight gain (Allison et al., 1999). Alternatively, when levels of synaptic dopamine increase, appetite decreases. This phenomenon also occurs clinically when patients are placed on certain medications for attention deficit hyperactivity disorder and is thought to be related to blockage of the dopamine active transporter 1 gene (*DAT1*; Capp, Pearl, & Conlon, 2005). Furthermore, research has also revealed this relationship between dopamine levels and changes in eating behavior in animal models. “Dieting” rats, modeled by time-sensitive restriction of sucrose, have alterations in levels of dopamine, dopamine receptors, and transport mechanisms, as compared to those with unrestricted access to sucrose (Bello,

Lucas, & Hajnal, 2002; Bello, Sweigart, Lakoski, Norgren, & Hajnal, 2003; Hajnal & Norgren, 2002).

Thus, in both preclinical and clinical models, any disruption in the balance of the dopaminergic system can result in disordered eating patterns. Consequently, individuals with alterations in their dopaminergic systems may overeat to raise their dopamine levels in an attempt to derive a pleasurable feeling from food. Although it may seem counterintuitive, researchers have hypothesized that overeating is an individual's attempt to compensate for a reduced dopaminergic response (Volkow, Wang, Tomasi, & Baler, 2013). Long-term, overconsumption leads to weight gain and to the development of obesity.

Dopaminergic Pathways

Dopamine is present throughout the brain, but it is concentrated in four major pathways: the nigrostriatal pathway, tuberoinfundibular pathway, mesolimbic pathway, and mesocortical pathway (Chinta & Andersen, 2005). The nigrostriatal pathway runs from the substantia nigra to the striatum, and it is mostly responsible for movement. When portions of this pathway are dysfunctional, the disturbance results in Parkinson's disease. The tuberoinfundibular pathway includes dopaminergic projections in the hypothalamus and the pituitary gland, and it is important for development and regulation of the hormone prolactin. However, research has not shown either of these pathways to be strongly associated with obesity. In contrast, the mesolimbic and mesocortical pathways, known as the "reward pathways," include dopaminergic regions related to impulsivity, self-control, and the pleasurable feelings associated with addictive behaviors and are strongly associated with obesity. For a more detailed overview of the functionality of all four dopaminergic pathways and a diagram of projections, please see Chinta and Andersen (2005).

Dopamine's association with obesity is attributed to the mesolimbic pathway, which originates in the ventral tegmental area and projects to the nucleus accumbens. These areas are in the midbrain and are outside our conscious control. In response to hunger cues (partly driven by hormones such as ghrelin, leptin, and insulin), the activity of dopaminergic neurons in the ventral tegmental area increases (Opland, Leininger, & Myers, 2010). The mesocortical pathway projects from the ventral tegmental area to the higher reasoning centers of the cerebral cortex that control reward and motivation. Typically, the two pathways are combined and referred to as the mesolimbocortical pathway because of the close interplay between reward mechanisms and pleasurable feelings. Research has shown the mesolimbocortical pathway to be associated with many types of rewarding experiences, but it is most strongly associated with fundamental pleasures such as sex and food and less strongly associated with higher order pleasures such as monetary, altruistic, and artistic pleasures (Kringelbach & Berridge, 2010).

Neuroimaging Evidence for the Relationship Between Obesity and the Dopaminergic Reward Pathways

Neuroimaging provides an important tool to study obesity because of its ability to localize brain areas involved in eating behavior. In particular, functional magnetic resonance

imaging data are valuable in that it display areas of increased blood flow (i.e., areas that are activated) during particular tasks. For instance, the insula and the striatum are commonly coactivated during presentation of food cues (Tang, Fellows, Small, & Dagher, 2012). The amygdala is activated during eating, perhaps due to the associated positive emotions. Additionally, researchers believe that the recall of memories and experience with food activates the hippocampus (Carnell, Gibson, Benson, Ochner, & Geliebter, 2012). Neuroimaging also allows comparisons of activation patterns between obese and normalweight individuals during the presentation of food cues. From these comparisons, we know that obese individuals show greater activation in the mesolimbocortical pathway than normal-weight individuals (Killgore & Yurgelun-Todd, 2005).

Another type of neuroimaging uses a variation of the traditional positron emission tomography (PET) scan to identify dopaminergic activity and dopamine receptors. For example, in one study using this technology, researchers showed that dopamine release correlates with the ratings of pleasantness experienced during food consumption (Small, Jones-Gotman, & Dagher, 2003). Another study found that when subjects were presented with food cues, increases in dopamine were correlated to the level of hunger subjects reported (Volkow et al., 2002). Studies of this type confirm that there are lower levels of dopamine receptors in the striatum of obese patients, such that the magnitude of the reduction is proportional to the increase in BMI (Haltia et al., 2007; G. J. Wang et al., 2001). This observation may indicate a reduction in the rewarding aspects of food intake, which may lead to overeating in compensation. The reduction in dopamine receptors is also related to decreased activity in the prefrontal cortex, which may indicate a reduction in self-control with regard to food intake for obese individuals (Volkow, Wang, Fowler, & Telang, 2008).

Neuroimaging has also revealed an overlap in neural activity between obesity and substance addiction, prompting the hypothesis that food addiction may play a role in the development of obesity. This overlap is not surprising, as many commonly abused substances act on the dopaminergic pathways in much the same way as highly palatable foods. An overlap in the activation patterns of dopaminergic pathways has also been shown between the development of obesity and addiction to smoking (Tang et al., 2012), cocaine, heroin, alcohol, and methamphetamine. All of these substances impair the functioning of dopamine receptors and reduce the amount of dopamine released in addicted individuals (Martinez et al., 2005; Volkow et al., 1997; Volkow, Fowler, Wang, & Swanson, 2004). Interestingly, obese individuals are less likely than normal-weight individuals to use illicit drugs (Blum et al., 2012), and if they do, they are at less risk for a substance use disorder in the future (Simon et al., 2006). These findings could indicate that obese individuals are achieving, by overeating, the reward that many drug users seek.

Genetic Evidence for the Relationship Between Obesity and the Dopaminergic Reward Pathways

There is accumulating evidence to support a relationship between obesity and dopamine receptor genes, dopamine transport genes, and genes involved in dopamine degradation. Alterations in any of these genes can change the levels of dopaminergic stimulation in the brain (Table 1).

Dopamine Receptor Genes

The dopamine receptor genes most widely implicated in obesity are dopamine receptor D2 (*DRD2*), dopamine receptor D3 (*DRD3*), and dopamine receptor D4 (*DRD4*). All of these receptors have seven transmembrane domains and are G-protein–coupled receptors. These three receptors are also classified as D2-like receptors, meaning that they inhibit intracellular cyclic adenosine monophosphate (cAMP) to suppress that signaling pathway (Baik, 2013).

DRD2—D2 receptors are the most abundant type of dopamine receptor in the brain (Baik, 2013). The A1 minor allele for a functional polymorphism (rs1800497, Taq1A) of *DRD2* is correlated with an overall reduction in the number of D2 receptors in the brain (Pohjalainen et al., 1998). This polymorphism has been associated with an overall “reward deficiency syndrome,” which presents as multi-substance or multi–high-risk-activity abuse in those lacking proper dopamine function (Blum, Liu, Shiner, & Gold, 2011). Neuroimaging data have confirmed the reduction in reward processing for people with this genotype (Pecina et al., 2012), and, as mentioned previously, the magnitude of the reduction in D2 receptors is proportional to the increase in BMI in obese individuals with the A1 allele (G. J. Wang et al., 2001). Additionally, the minor allele is associated with an increased percentage of body fat (Chen et al., 2012).

Moving down the *DRD2* gene by roughly 17 kilobases, another polymorphic site called C957 T (rs6277) also affects the function of the dopamine receptor. The T allele (vs. C) is associated with reduced levels of *DRD2* mRNA overall and also with reduced translation of that mRNA into receptor protein (Duan et al., 2003). PET scans have confirmed that this reduction results in lower levels of D2 receptors in the striatum of individuals with this allele, and the receptors that are present show lower binding affinity for dopamine (Hirvonen et al., 2004). When this allele is combined with the influence of the Taq1A allele and age, it explains 40% of the variance in the numbers of D2 receptors throughout the brain.

Another 63 kilobases down the gene, rs12364283 is in a conserved suppressor region (Y. Zhang et al., 2007). Not surprisingly, when this area is disturbed by the change into the minor T allele, the result is increased transcription and receptor density. This observation is especially interesting, as it supports Cashion et al.’s (2013) results. To summarize that study, RNA expression changes in five genes related to dopamine secretion were associated ($p = .0004$) with weight gain at 6 months post kidney transplantation. Based on these two pieces of evidence, it is logical to infer that the expression changes seen in RNA could be created by variations in the regulatory regions in the DNA for those genes.

DRD3—The functional Ser9Gly polymorphism (rs6280), located within the *DRD3* gene on the long arm of Chromosome 3, has been associated with increased dopamine affinity. Specifically, the glycine allele causes the dopamine receptor to have an affinity for dopamine that is increased 5-fold as compared to the ser allele (Jeanneteau et al., 2006). Heterozygosity for this polymorphism is associated with higher scores on impulsiveness (Limosin et al., 2005). Clinically, the glycine allele has been associated with smoking

(Huang, Payne, Ma, & Li, 2008), cocaine abuse (Comings et al., 1999), and schizophrenia (F. Zhang et al., 2011).

DRD4—The dopamine receptor type 4 gene is a relatively short gene (about 3,400 base pairs), and much of the variability in this gene can be captured through one 48-base-pair variable number tandem repeat (VNTR) in Exon 3. This VNTR can have between 2 and 11 repeats of this 48-base-pair segment. Alleles are referred to by the number of repeat segments. Usually, the 7-repeat allele is established as a risk allele for many different disorders, including attention-deficit/hyperactivity disorder and schizophrenia. In preschool children, carriers of the 7-repeat allele consumed more fat and protein than did those possessing different repeat lengths (Silveira et al., 2013), suggesting that the type of food preferred could be dependent on dopaminergic genotype.

In vitro studies have shown that the 7-repeat allele binds less tightly to dopamine due to alterations in the activity of cAMP (Asghari et al., 1995). The 7-repeat allele greatly reduces cAMP levels; however, another allele, the 2-repeat allele, is nearly as effective at this reduction. Reist et al. (2007) have suggested that, due to evolutionary and biochemical similarities, the 2- and 7-repeat alleles should be grouped together as risk alleles. These authors found a significant difference in the degree of novelty-seeking behavior when the alleles were grouped this way instead of in the more common short-versus-long allele comparison.

Dopamine Transporter Gene

Neurotransmitter transporters are cell membrane portals that remove neurotransmitters from the synapse and regulate the strength and duration of neurotransmission. In the case of dopamine, there is only one transporter, the dopamine active transporter, solute carrier family 6 (neurotransmitter transporter), member 3 (*SLC6A3*). This same gene is also called *DAT1*.

In the 3' untranslated region of *SLC6A3/DAT1*, there is a VNTR that greatly affects dopamine clearance from the synapse. Heinz et al. (2000) have suggested that this VNTR alters translation of the mRNA into protein. However, evidence regarding the implications of each variant is somewhat mixed. It has been shown that the nine-repeat allele increases transcription of *SLC6A3/DAT1*, resulting in more transporters. As a result, more dopamine undergoes reuptake by the presynaptic neurons and there is less dopamine available to bind to postsynaptic neurons (Blum, Chen, et al., 2011). However, other researchers have shown that subjects with the 9-repeat allele have a lower number of dopamine transporters compared to those with the 10-repeat allele (Heinz et al., 2000).

Dopamine Degradation Genes

Other important dopaminergic genes associated with reward include catechol-o-methyltransferase (*COMT*) and monoamine oxidase isomers A and B (*MAOA* and *MAOB*). These genes code for enzymes that break down dopamine and, along with reuptake of the neurotransmitter, reduce the amount of dopamine available in the synaptic cleft. When these

degradation mechanisms are altered, the levels of available dopamine could either increase or decrease.

COMT—Catechol-o-methyltransferase is associated with reward through its influence on dopamine availability in the cortex. It is the only enzyme that can act to methylate synaptic dopamine and begin the breakdown process. The met allele of a common polymorphic site (Val108/158Met, rs4680) in the COMT gene causes this enzyme to have reduced activity (Caldu et al., 2007). As a result, individuals with this allele might seek out experiences to induce the reward “high.” This polymorphism has been suggested as a marker, and potential drug target, for addiction (Blum & Gold, 2011). In addition, the rs4680 met allele is associated with increased abdominal obesity in men (Annerbrink et al., 2008). However, Galvao and colleagues (2012) found an increase in consumption of high-fat and high-sugar foods for those with the val allele.

Approximately 64 kilobases away from rs4680 is a synonymous G/C variant, rs4818 (Leu136Leu). Although there is no functional change in the protein produced from this gene, the C allele of this polymorphism has been associated with increased BMI (S. S. Wang et al., 2007). It appears likely that this polymorphism acts as a marker in linkage disequilibrium with another causal variant, perhaps rs4818 noted previously.

MAOA—Monoamine oxidase A is an enzyme that deaminates dopamine, changing the overall bioavailability of the neurotransmitter. It and its partner MAOB are located in the mitochondria of neurons and break down dopamine that has already been removed from the synaptic cleft. A 30-base-pair VNTR of the *MAOA* isoform of this gene is in the promoter region (Camarena et al., 2004). The promoter region of a gene is where the initial binding of transcription proteins takes place, so polymorphisms in this area are particularly influential on gene product availability. In the case of this VNTR, repeat alleles from 2 to 5 have been recorded. The most common alleles are the 3-, 3.5-, and 4-repeat alleles, although there is variation in the frequencies within certain racial and ethnic groups (Sabol, Hu, & Hamer, 1998). Individuals with the 3.5- and 4-repeat alleles show greater mRNA production than those with the other alleles (Sabol et al., 1998), and boys with the longer repeats have a greater preference for high-fat and sugary foods than those with shorter repeats (Galvao et al., 2012). Additionally, shorter alleles are in transmission disequilibrium in obese families (Camarena et al., 2004).

MAOB—The A allele of a single nucleotide polymorphism (SNP) in the MAOB isoform of this gene (B-SNP13, rs1799836) correlates with higher dopamine levels in the brain (Balciuniene, Emilsson, Orelund, Pettersson, & Jazin, 2002). Although it is important to note that MAOA and MAOB have different distributions in tissues, they have identical activity for dopamine degradation. Increased activity in one isoform could potentially compensate for reduced activity in the other (Need, Ahmadi, Spector, & Goldstein, 2006). The activity of both enzymes must be taken into account. However, adipose tissue taken from obese subjects has lower expression levels for both types of monoamine oxidases than tissue taken from nonobese subjects (Visentin et al., 2004), so a “double-hit” in both MAOA and MAOB could potentially have large effects on weight in an additive way. Need, Ahmadi, Spector, and Goldstein (2006) found a significantly higher number of low-activity

genotypes in obese as compared to nonobese subjects, although the MAOB lowactivity polymorphism was not significantly associated with weight or BMI on its own.

Conceptual Model

In summary, there is strong experimental evidence for the association between genes related to dopamine and changes in weight. This evidence indicates that the association occurs at multiple locations in dopamine production pathways and suggests that changes in weight could be genetically driven at any of these points. Furthermore, this information fits into the larger body of knowledge about weight gain leading to obesity, namely, that factors such as age, race, gender, physical activity, dietary intake, and medications can also contribute to increased weight. We have combined the genetic factors with the demographic and behavioral/environmental factors to create a conceptual model for the development of obesity, as illustrated in Figure 1.

On the right-hand side of the wheel, the environmental factors of physical activity, diet, and medication are shown. Certainly, an increase in physical activity and a healthy diet reduce weight and the risk of comorbidities commonly associated with obesity for most individuals (for an excellent review, see Swinburn, Caterson, Seidell, & James, 2004). Although not explicitly illustrated by this model, genotype (and expression of that genotype) can influence an individual's unique response to changes in physical activity and diet. For example, expression of the melanocortin 4 receptor (*MC4R*) has been associated with weight change (Cashion et al., 2013) and also has a variant genotype associated with physical activity (de Vilhena e Santos, Katzmarzyk, Seabra, & Maia, 2012). While research has revealed some promising genetic associations regarding individuals' responses to changes in physical activity and diet, most have had small effect sizes, and the inherent noise of this type of data also tempers their promise at this time. Furthermore, researchers are only just beginning to understand the biochemical pathways influenced by some of these gene associations. Regardless, physical activity and diet remain important factors to consider for weight gain leading to obesity.

Certain medications can have side effects related to changes in weight. For instance, some medications for attention deficit hyperactivity disorder are associated with weight change (Capp et al., 2005). Interactions between medications may also amplify weight-related side effects. Again, though not illustrated by the model, genetics play a role in an individual's response to medications. The field of pharmacogenomics shows great promise for uncovering and reducing the impact of some of these associations, but for now, medications remain an influential factor in the development of weight gain leading to obesity.

Race, gender, and age may also influence weight gain. Cultural perceptions of beauty may influence racial differences in risk for developing obesity, but genetic differences among races are also important. For instance, regarding SNPs, different races have skewed minor-allele frequencies for various obesity-related genes. This skewness could make some races more or less likely to gain weight. Gender plays a role in the distribution of the weight gained (i.e., an android vs. gynoid weight distribution), which then can influence the risk for associated comorbidities. And finally, large epidemiological studies have shown that people

tend to gain weight as they age, with weight peaking at late middle age (Cornoni-Huntley et al., 1991). Thus, the factors of race, gender, and age cannot be ignored when considering obesity.

The box on the left of the model illustrates the dopaminergic genetic contributions to personality and the reward brain regions, which then influence weight gain and obesity, as we have discussed in this article. We selected these particular genes due to associations with weight gain or obesity previously reported in the literature, as discussed previously. Differences in genotype for these genes can partially explain individual variation in susceptibility to weight gain. Each gene depicted has polymorphisms that influence the dopamine levels in the brain by affecting the overall bioavailability of the neurotransmitter, altering dopamine transport, or regulating dopamine receptors. As mentioned previously, binding of dopamine to its receptor sites induces a pleasurable feeling, and this binding is responsible for some of the rewarding experience that occurs when an individual eats highly palatable food (Baik, 2013). Additionally, alterations within the transport system can cause alterations in the binding rate, based on whether the dopamine is more likely to be transported into the postsynaptic neuron or undergoing reuptake into the presynaptic neuron.

The conceptual model has value for the understanding of obesity and, most importantly, for the treatment for obesity. Namely, dopaminergic pathways have become pharmaceutical targets for the development of anti-obesity medications. But, as the model shows, future research on treatments for obesity should address both environmental and genetic factors in order to give the greatest chance for long-term success of weight loss treatments.

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Figure 1.

A conceptual model of weight gain leading to obesity. The spokes dividing the factors leading to obesity are composed of broken lines to indicate the interaction among them, similar to the model proposed by Ziauddeen, Farooqi, and Fletcher (2012). We altered the categories from the original model to reflect the information we have presented in this review as well as additional clinical observations that we have made. Additionally, we represented the outside of the wheel with another broken boundary to represent the influence that as-yet-unidentified factors could have on the outcome of weight gain leading to obesity. Adapted by permission from Macmillan Publishers Ltd: Ziauddeen, H., Farooqi, I. S., & Fletcher, P. C. (2012). Obesity and the brain: How convincing is the addiction model? *Nature Reviews Neuroscience*, 13(4), 279–286. Copyright 2012.

Table 1

Neurogenetic Evidence for a Relationship Between Obesity and Dopamine.

Gene Symbol	Gene Name	Variant	Selected Evidence
DRD2	Dopamine receptor, type 2	rs1800497	Blum, Liu, Shriner, and Gold (2011); Chen et al. (2012); Pecina et al. (2012); Pohjalainen et al. (1998); G. J. Wang et al. (2001)
		rs6277	Duan et al. (2003); Hirvonen et al. (2004)
		rs12364283	Y. Zhang et al. (2007)
DRD3	Dopamine receptor, type 3	rs6280	Jeanneteau et al. (2006); Limosin et al. (2005)
DRD4	Dopamine receptor, type 4	VNTR	Asghari et al. (1995) and Reist et al. (2007)
SLC6A3/DAT1	Dopamine active transporter	VNTR	Blum, Chen, et al. (2011); Heinz et al. (2000)
COMT	Catechol-o-methyltransferase	rs4680	Blum & Gold (2011); Caldu et al. (2007)
		rs4818	S. S. Wang et al. (2007)
MAOA	Monoamine oxidase A	VNTR	Camarena et al. (2004); Galvao et al. (2012)
MAOB	Monoamine oxidase B	rs1799836	Balciuniene, Emilsson, Orelan, Pettersson, and Jazin (2002)

Note. VNTR = variable number tandem repeat.