Review Article

To Eat or Not To Eat: The Neurobiological Substrates Guiding Maladaptive Decision-Making in Obesity

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Abstract

Obesity is an increasingly prevalent disease characterized by excess food consumption despite adverse consequences that include a myriad of life-threatening health conditions. Current strategies to treat this condition rarely induce long-term weight loss in part because they do not address the psychological drive to consume excess food. Understanding the mechanisms of decision-making processes that ultimately underlie overeating may lead to a better understanding and treatment of this complex disease. In this review, we summarize functional studies demonstrating the neurological circuits that encode discrete facets of decision-making and discuss how these processes may be abnormal in obesity. Our analysis draws striking parallels between the phenotypes and underlying neurological mechanisms of obesity and drug addiction. Finally, because functional changes in brain activity are reflective of underlying molecular events that influence neuronal plasticity, we suggest an epigenetic model for obesity that has proven relevance in mediating neuroplastic and behavioral changes in the context of substance abuse.

The most recent edition of the American Psychiatric Association's Diagnostic and Statistic Manual of Mental Diseases (DSM-V) for the first time formally classifies binge eating as a psychiatric eating disorder. Although obesity and overeating were not added to the manual, emerging evidence suggests that obesity is influenced by psychological variables and long-term functional changes in the brain that contribute to maladaptive decision-making processes regarding food consumption. With over 30% of Americans meeting clinical criteria for obesity (body mass index over 30 kg/m^2), this condition is recognized as an alarming and escalating public health concern [1]. It is the leading cause of preventable death worldwide [2]. Treatment for obesity typically includes strategies to reduce caloric intake, including behavioral modifications such as diet, exercise, and counseling programs as well as pharmacological treatments aimed to decrease fat absorption and suppress appetite. Despite these interventions, success rates of long-term weight loss maintenance remain staggeringly low [3]. Even with highly invasive bariatric surgery to reduce stomach size, patients still experience elevated high fat and calorie dense food cravings [4]. Ultimately, most patients regain a significant amount of weight after surgery [5]. In order to improve obesity treatment, it is necessary to understand the biological mechanisms that drive excess food consumption.

Decision-making is the cognitive process of selecting a course of action among several alternatives. The end goal of a rational decision-making process is to maximize the chance of an advantageous outcome while minimizing the risk. However, this process often involves weighing immediate rewards against long-term negative consequences. Psychological variables such as the perceived needs, values, preferences, and emotional state of an individual can influence decision-making, often unconsciously. A growing body of evidence suggests that decision-making processes are adversely affected in obese individuals [6]. Obese individuals perform more poorly compared to lean subjects [7] and even to drug addicts [8] on a gambling task where decision-making is evaluated by allowing participants to select from separate decks of cards that will consistently lead to either rewards or losses. Brain processes that suppress the pursuit of short-term rewards in the anticipation of adverse long-term consequences are especially subject to dysregulation in societies with ready access to palatable, calorie-dense foods [8]. Consideration of the brain mechanisms that assimilate sensory, cognitive, and psychological cues to resolve decisions concerning food consumption may therefore lead to a greater understanding of abnormal decision-making processes in obesity.

Functional magnetic resonance imaging (fMRI) has lent

great insight into the neural substrates that subserve decision-making processes. The prefrontal cortex (PFC), a higher order cortical structure that is critical for decision-making, is divided into multiple subregions that rely on distinct constructs to inform decisional operations. Within the PFC, the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) are reciprocally active during decision-making done independently or guided by an experimenter, respectively [9]. Functional mapping studies of subjects with brain lesions showed that the ACC and another PFC region, the dorsolateral PFC (dlPFC), are involved with cognitive control (use of task rules including response inhibition, conflict monitoring, and switching) while the OFC is more closely associated with value-based decision-making (reward properties) [10]. These findings underscore a remarkable functional-anatomical specificity in the human PFC. Lesions to the ACC in macaque monkeys result in long-term impaired

Figure 1 A simplified schematic of the brain signaling networks that mediate distinct facets of the decision-making process that pertain to food intake. Perception of stimulus value (purple) is mediated by activation of the reward system, which consists of mesolimbic dopamine projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) as well as mesocortical projections to prefrontal cortex (PFC) subregions (ventromedial PFC, vmPFC; orbitofrontal cortex, OFC). Opposing actions of the dorsolateral PFC (dlPFC) weigh the health value of a food compared to the individual's preference for it. Self-control (green) wins over preference (dark blue) when signals from the dlPFC-M are relayed to the vmPFC by way of the inferior frontal gyrus (IFG). In contrast, hyperactivity of the dlPFC-U reinforces the preferences of an individual regardless of the health attributes. The dlPFC and vmPFC also work together to compute emotional states that can lead to impulsive behavior. Emotional reactions to stimuli are channeled through the sensory cortex to the (AMY) and ultimately to the brainstem in order to initiate an appropriate autonomic response. This information is fed back to the PFC, where the dlPFC and vmPFC hold a representation of the emotional response linked to the bodily state (somatic marker theory, light blue). This representation influences decision-making upon subsequent exposure to the same stimulus. A fifth region of the PFC, the anterior cingulate cortex (ACC) computes cognitive variables based on rules assembled from historical choices linked to outcomes (orange).

decision-making in reinforcement guided tasks, suggesting the ACC guides voluntary choices based on the history of actions and outcomes [11]. Patients with OFC lesions have difficulty in the gambling task, a test based on evaluation of reward [12]. Both the ACC and OFC have been shown to be hyperactivated in response to food cues in obese individuals compared to controls [13-15], suggesting that obese individuals have alterations in the neural circuits that control both cognitive and value-based decision-making.

In order to make decisions that are beneficial in the long term, it is essential that an individual exert self-control over immediate preferences if the long-term outcome is disadvantageous. Impaired self-control favors the intake of substances of abuse or consumption of palatable, energy rich diets and may thus promote the development of addiction and obesity [16,17]. A study by Hare et al. [18] using fMRI showed that health aspects influence an individual's dietary decisions through engaging specific subregions within the PFC, namely the ventromedial PFC (vmPFC), dlPFC, and inferior frontal gyrus (IFG). Within the dlPFC, the authors identified 2 further subregions. The dlPFC-M weighs choices mainly based on health attributes, while the dlPFC-U encourages the ingestion of palatable foods regardless of their health value [19]. Based on functional connectivity and dynamic causal modeling analyses, the authors suggested a four-node circuit for self-control during dietary decision-making based on health attributes. This circuit consists of the opposing actions of the dlPFC-M and dlPFC-U, which send projections to the IFG and ultimately to the vmPFC to moderate the stimulus value of tasty food by health aspects [19]. The contribution of these PFC subregions on an obese subject to make healthy dietary choices remains to be clarified in future studies.

Obese individuals may have an inability to cope with negative emotions that contributes to overeating behavior when distressed [20]. Negative emotional states are higher in gastric bypass patients compared to healthy controls and significantly correlate with poorer BMI reduction after surgery [21]. Obese individuals also exhibit impulsive behaviors, which may be a predisposing risk factor for future obesity in adolescents [22]. Emotions are linked to impulsive, poorly planned behaviors through brain networks that mediate the decision-making process. According to the somatic-marker hypothesis, emotions elicited during the deliberation of future consequences help to classify behavior as being advantageous or disadvantageous [23]. This process first involves the synthesis of sensory influences that are channeled through the sensory cortex to the amygdala, a region that mediates emotion and fear perception. A bodily response is then signaled through the brainstem to modulate processes such as autonomic activity. The dlPFC and vmPFC hold internal representations of the bodily response linked to the initiating behavior. These brain regions reactivate bodily responses during decision-making processes where the same behaviors are contemplated. Disruption of this somatic-marker circuit can lead to impulsive behaviors. Patients with vmPFC lesions are unable to advantageously assess future consequences of their decisions, such that their behavior is guided by the immediate contingency [24]. Patients with vmPFC damage also exhibit abnormal autonomic responses to socially meaningful stimuli, but have normal responses to unconditioned stimuli
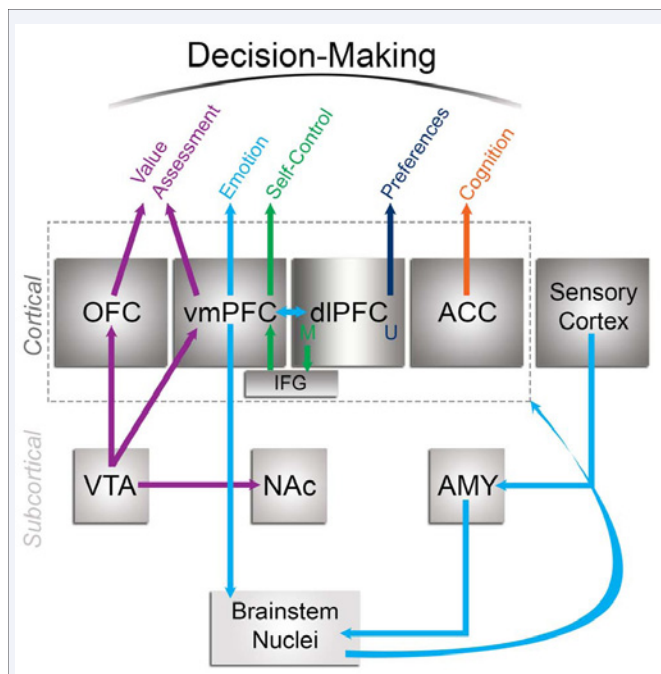
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[25]. Collectively, these studies suggest the PFC is critical for higher-order encoding of the links between emotion and bodily states that guide appropriate decisions regarding advantageous behavioral outcomes. In response to food cues, an fMRI study of obese individuals found that activity in the amygdala was found to be positively correlated with impaired satiety scores while PFC activity was negatively correlated [26]. This suggests a model whereby obese individuals become hyperemotional in response to food cues but cannot activate brain circuitry that would normally inhibit impulsive behaviors.

Emotional/bodily states are also mapped within the reward circuitry of the brain that consists of dopaminergic projections from the ventral tegmental area (VTA) to the striatum. The reward pathway unconsciously biases future decision-making toward choices deemed as advantageous [23]. The majority of studies concerning hunger and food motivation have focused on endocrine signaling. Endocrine hormones regulate food intake in part through actions on brain regions that mediate homeostatic control, that is, regions such as the hypothalamus that control energy balance. Increasing evidence suggests that a more complete understanding of the endocrine effects on hunger perception can be achieved by consideration of non-homeostatic brain regions [27]. A series of studies using fMRI examined such effects for leptin, a key endocrine regulator and potent inhibitor of food intake, in subjects with hyperphagia and obesity due to congenital leptin-deficiency. In these leptin-deficient subjects, activation of the nucleus accumbens (NAc) was positively correlated with likeability of food images in both fed and fasted states [28]. After treatment with leptin, this association was observed only in the fasted state similar to healthy controls. Activity in reward pathway circuitry including the VTA, NAc and the OFC correlated with long-term benefits of leptin replacement therapy [29,30]. These findings suggest that leptin, and potentially other endocrine hormones, modulate feeding via actions on higher order brain circuits involved in reward perception.

The reward pathway is most often associated with drugs of abuse. Human and animal studies of substance abuse have shown that the reward circuitry is characterized by gene expression, synaptic plasticity, and functional changes that underlie clinical features of dependence [31]. In addition to abnormalities within the reward pathway, studies suggest that substance dependent individuals exhibit a deficit in somatic/emotional encoding guided by the vmPFC as reflected in poor performance in a gambling task [7]. Despite being aware of adverse medical, social, legal, and health outcomes associated with substance abuse, dependent individuals are unable to control their use. This draws striking parallels to the inability of obese individuals to control caloric intake despite poor body image, reduced quality of life, and serious secondary health consequences [32]. The self-reported rate of lifetime substance abuse disorder in bariatric surgery patients was found to be more than double the rate in the general population [33]. These studies suggest that the neural substrates of substance dependence may share common mechanisms with pathways that underlie pathological food consumption. Numerous studies have led insight into the molecular signaling pathways that give rise to synaptic plasticity changes and functional alterations in response to drugs of abuse.

Consideration of such knowledge may also lend insight into the mechanisms that precede functional changes in the brain of obese individuals.

Animal studies have shown that epigenetic mechanisms mediate addictive behaviors in response to repeated exposure to drugs of abuse. Since drug addiction and binge eating/excessive eating share similar neurobiological correlates, chromatin remodeling through histone modifications, DNA methylation, and noncoding RNA expression may also play a role in the development of obesity. The contribution of these epigenetic modifications to addiction-related behavioral abnormalities was demonstrated in genetic and pharmacological animal models with subsequent changes in DNA and/or histone methylation. Epigenetic modifications could influence substance abuse behaviors in three possible manners [34]: i) by causing gene expression changes that directly influence behavior; ii) by altering inducibility of genes in response to environmental exposures that would affect an individual's vulnerability to addiction throughout their lifetime [35]; and iii) by modifying the epigenome of the gametes, which would affect the susceptibility of offspring for developing addiction. Examples of epigenetic modifications in response to drug exposure in animals involve altered levels of acetylated histone H3 and H4 [36-38], histone H3 lysine 9 dimethylation (H3K9me2) [39-41], and histone H3 lysine 9 trimethylation (H3K9me3) [42] in the NAc, a key brain reward region. DNA methylation may further modulate behavioral responses to drug exposure as concluded from animal studies with genetic or pharmacological inactivation of DNA methyltransferase activities inside the NAc [43,44]. These epigenetic changes can lead to gene expression changes that underlie morphological plasticity and behavioral adaptations. For example, cocaine-induced demethylation of H3K9me2 increases dendritic spine plasticity in the NAc and enhances cocaine preference in rodents [41]. Future studies are needed to clarify whether epigenetic mechanisms may induce neuroplastic changes that influence decision-making in the context of obesity.

Epigenetic mechanisms are especially important during neurodevelopment when the brain has a heightened sensitivity to environmental exposures that mediate long-term behavioral patterns. For example, adolescent exposure to cannabinoids disrupts H3K9 methylation in the NAc during development and increases susceptibility for heroin self-administration later in life [45]. Prenatal exposure to cannabis alters epigenetic regulation of dopamine receptors that contribute to increased sensitivity for opiate reward in adulthood [46]. Consistent with this developmental epigenetic model, chronic exposure to energy-dense, palatable food during childhood may increase the risk for long-term behavioral changes and poor decision-making in children. Obese compared to lean children showed higher activation of the dlPFC and in the OFC in response to food pictures [47,48]. In addition, obese children displayed blunted post-meal reduction of activation in the PFC and NAc [47]. These observations suggest that obesity in children is associated with abnormalities in neural circuitry mediating food motivation. These neurodevelopmental abnormalities may, at least in part, be prefaced by epigenetic mechanisms that contribute to altered decision-making throughout life. Yet another parallel between obesity and drug addiction is the influence of stress on food

and drug-seeking behavior. Drug addiction is characterized by a heightened sensitivity to stress, which seems to be mediated at least in part through epigenetic mechanisms. For example, cocaine-induced H3K9 demethylation in the NAc potentiates depressive-like behaviors and confers increased sensitivity to stress [49]. A growing body of evidence suggests that early life abuse leads to long-term changes in stress-associated and neuronal plasticity pathways that are mediated by alterations in DNA methylation [50-52]. Epigenetic changes can be highly pathway specific, as demonstrated by a combined genetic-adolescent stress rodent model of schizophrenia where the glucocorticoid promoter was found to be specifically methylated in mesocortical, but not mesolimbic, dopaminergic neurons within the reward pathway [53]. Exposure to chronic stress, especially when coupled with the availability of calorie-dense foods, is associated with a greater preference for high fat, sugar rich foods and is causally linked to weight gain in humans [54,55]. These findings are consistent with the hypothesis that epigenetic mechanisms may contribute to stress-induced overeating in obese individuals. Given the findings of stress-induced epigenetic changes within highly specific neural circuits, it is possible that brain networks involved with distinct aspects of decision-making may be differentially epigenetically modified in obesity.

The fMRI studies summarized above have lent great insight into the neurobiological correlates of the decision-making process. Ultimately, however, neuroplastic alterations must underlie functional changes in brain activity associated with impaired decision-making processes. Endocrine hormones known to modulate food intake have been shown to induce synaptic plasticity changes in brain regions controlling homeostatic feeding [56-58]. Given the fMRI studies of leptin-mediated changes in brain activity of non-homeostatic brain regions, future studies are needed to determine whether these circuits may also be subject to endocrine-mediated synaptic plasticity. Epigenetic-induced changes in gene expression and synaptic connectivity within the reward circuitry are known to mediate clinical characteristics that characterize substance dependence. Similar mechanisms could be investigated in the context of obesity by studying neural networks that subserve cognitive, value based, self-control, emotion/impulsivity, reward perception, and stress response aspects of decision-making. Such studies could illuminate the developmental, environmentally sensitive, and lifelong mechanisms that drive excess food consumption in the face of adverse consequences.

ACKNOWLEDGMENTS

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