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Individual Differences in the Neurophysiology of Reward and the Obesity Epidemic

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Abstract

The obesity epidemic has unfolded in a matter of decades, not millennia, and cannot therefore be attributed to a drift in the genome. Rather, the temporal characteristics of the epidemic more closely track environmental and lifestyle changes, such as reduced physical activity, increased availability of palatable and caloric foods and drinks, and increased acceptance of eating outside of meal time (among others). One important observation is that not everyone is becoming obese. This suggests that individual factors interact with recent environmental changes to predispose some to overeat (1). One hypothesis that has been gaining traction in the neuroscience community is that individual differences in the neural encoding of foods may predispose some to overeat in the presence of a surplus of caloric palatable foods and drinks (2-6). The aim of this paper is to highlight several possible ways by which individual differences in the neurophysiology of food reward may lead to overeating.

Keywords

amygdala; insula; dorsal striatum; prefrontal cortex; feeding

Introduction

Food reward is multifaceted (7), resulting in numerous ways for individual differences to impact upon eating behavior. Foods and beverages are multisensory stimuli comprising taste, retronasal olfaction, and oral somatosensory experiences, such as a food's viscosity and/or temperature. The combination of these inputs give rise to emergent flavor perceptions (8), and the pleasure derived from flavor and eating is highly dependent, not only upon the physical attributes of the independent sensory stimuli, but also upon how they are combined, upon the associations that are formed between these sensory stimuli and their post-ingestive effects (9), and upon the internal state of the organism (10). Individual differences in any aspect of food liking, resulting from experience or genes, may give rise to vulnerability to overeat in an environment where food is engineered to deliver pleasure.

The sight and aroma of food are also powerful sensory cues that impact flavor and guide feeding behaviors. However, these sensations are likely to have more of an impact on incentive coding of food rather than the perceived pleasure of foods. This is because, in contrast to flavor, which is experienced during eating and thus associated with pleasure (or displeasure), the sight and smell of foods provide information about food availability, and as such impact feeding by eliciting approach behavior commensurate with the incentive value of the cue. The incentive value of food cues is also influenced by experience and internal state and has been proposed

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to comprise distinct implicit and explicit processes (11). The aim of this mini review is not to review in detail all of the ways in which individual differences in encoding food may lead to overeating but rather to highlight several mechanisms that have already received some experimental support.

In 1983 Weingarten showed that conditioned cues elicit feeding in sated rats (12). The experiment consisted of two phases. In the conditioning phase rats were brought to an experimental cage while hungry and learned that when a buzzer was played they could press a lever and receive food. Over time the rats associated the buzzer with lever-pressing for food, as evidenced by decreasing latency before which the animal started feeding after the buzzer was sounded. On the experimental day the rats were fed to satiety before they were brought to the experimental cage where food was freely available. Initially, the sated rats did not eat. However, when the buzzer was played the rats immediately began to eat. In other words, a food cue caused sated rats to eat. This finding is significant because it demonstrated that factors other than those associated with energy depletion can cause food intake.

It is easy to think of anecdotal parallels of “cue-potentiated feeding” in humans. A passing dessert cart induces a sated individual who planned not to order dessert to succumb and order the triple chocolate fudge cake. Indeed theorists have long postulated that sensitivity to the external environmental cues (5) (more recently termed “cue-reactivity” (13)) override homeostatic signals to promote overeating in environments where food cues abound.

Work by Goricia Petrovich and her colleagues in rodents has shown that expression of cue-potentiated feeding is dependent upon connections between the basolateral amygdala and lateral hypothalamus (14). Accordingly, there is now a substantial neuroimaging literature showing that the amygdala responds to food cues (15-21). A key characteristic of cue-potentiated feeding is that the cue is predictive of the receipt of food reward. We therefore set out to test whether amygdala response to food aromas would be greater for those food aromas that predicted immediate delivery of their associate liquid food (19). In two separate studies we found that, as predicted, the amygdala responded preferentially to the predictive food odors compared to the similarly intense and pleasant non-predictive food odors. Notably, the response to the predictive food odor was also greater than the response to the receipt of the liquid food it predicted; again despite the fact that intensity and pleasantness ratings for the aroma and its drink were similar. The amygdala was only one region within a larger network, including the ventral pallidum, thalamus, midbrain, operculum and ventral striatum, which showed this selective response for food cues compared to food receipt. Other regions, such as the anterior dorsal insula, showed the reverse effect, responding preferentially to food receipt compared to food cues, and a third pattern of response reflected sensitivity to both cues and receipt. Importantly, the amygdala not only responds preferentially to food cues but there is also data to suggest that it selectively represents the reward value of cues compared to receipt. For example, the amygdala is sensitive to the devaluation of food cues by eating to satiety (16-18) but not of food receipt (22,23). Based upon this solid evidence for the role of the amygdala in non-homeostatic, cue-responsive eating, it is proposed that individual differences in the neural circuits within the amygdala that are important for learning about the incentive properties of food cues predispose some to overeat. This hypothesis is consistent with the incentive-sensitization theory of drug addiction, which proposes that incentive learning plays a key role in compulsive drug taking (24,25) and with data showing that overweight versus lean children consume more calories after exposure to food cues (26). It has also received some support from recent studies showing that 1) individuals who score high on measures of trait reward sensitivity also show enhanced responses in the amygdala (among other regions) to food cues (15), and 2) that amygdaloid response to food cues is hyper-responsive in obese individuals (27) and in individuals with Prader-Willi syndrome, which is characterized by hyper-phagia (28). An important question that remains to be answered is whether these

increased responses in the amygdala reflect enhanced incentive learning. In other words, is the enhanced response in the amygdala to a food cue a consequence of more efficient conditioning between cues, such as pictures or odors, and the rewards they predict? Further, do these responses, or does conditionability, predict future weight gain?

Heightened cue-reactivity has been proposed to interact with trait impulsivity to predispose individuals to overeat (29). The idea that dysfunctional appetitive behavior results from an interaction between deficient prefrontal inhibitory circuits coupled with heightened responses in circuits coding incentive value has also been proposed as a mechanism for compulsive drug use. Jenstch and Taylor proposed that: “Drug-seeking behavior may result from two distinct, but inter-related, phenomena that involve impulsivity. First, the disorder could be characterized by enhancement of the potency of the impulse (increased salience of the rewarding and/or reinforcing qualities of the desired drug/stimulus). Secondly, the ability actively to inhibit the impulse, at the cognitive level may be diminished.” Neuroimaging studies of feeding consistently report differential activity in regions of the brain that are thought to be important for inhibitory control as a function of BMI, such as the orbitofrontal cortex, dorsal and ventral lateral and medial prefrontal cortex (4,30,31). Reduced grey mater volumes have also been identified in the prefrontal cortex of obese versus lean humans (32). Atrophy in the right ventral insula, striatum and OFC in patients with frontotemporal dementia, has been associated with compulsive overeating despite recognized satiety (33). Conversely, successful dieters show increased resting regional cerebral following ingestion of a meal in the dorsal lateral prefrontal cortex, which correlates positively with dietary restraint (34). Thus, in line with the Jentsch and Taylor model of addiction, it is proposed that heightened response in regions representing the value of conditioned cues interacts with decreased inhibitory signals from prefrontal regions to promote overeating (4). Future studies using analysis techniques to examine the effective connectivity between regions (e.g. psychophysiological interaction analysis) and the dynamic interplay of networks (e.g. dynamic causal modeling) will be important for evaluating this hypothesis. For example one could ask whether it is the relative response of amygdala vs. prefrontal cortex that is the best predictor of body mass or future weight gain.

A third hypothesis, which has received considerable support, is that obese individuals have hypofunctioning reward circuitry, and that it is this blunted reward response that leads them to overeat in an effort to compensate for this deficiency (35). The possibility that hypo-functioning reward circuits drive overeating appears, at first glance, at odds with the heightened cue-reactivity hypothesis discussed above. However, it is widely recognized that food reward is multifaceted (e.g. (36-42) and that there may be both hypo- and hyperactive responses. For example, applying Berridge and Robinson's incentive-sensitization theory of drug addiction (24) to overeating, Raynor and Epstein propose that food wanting and liking operate in tandem in the development of reinforcing value of food, but that over repeated presentations of food liking decreases, while wanting increases (43). Similarly, Davis and colleagues have suggested that people who score high on a measure of sensitivity to reward may be at risk for chronic over-consumption, which then leads to neural adaptations in the dopamine system that result in an anhedonic state. Consistent with this hypothesis they found evidence for heightened sensitivity to reward in overweight individuals and anhedonia in obese individuals (2). In terms of neural substrates, obese rats have low basal dopamine levels and reduced D2 receptor expression (44,45). Similarly, in humans Wang and associates (2001) found that D2 receptors are reduced in the striatum in morbidly obese individuals, and that the reduction is proportional to their body mass index (BMI) (46). More recently we found that blood oxygen level dependent (BOLD) response in the dorsal striatum to the receipt of a palatable milkshake is decreased in overweight and obese adolescent girls compared to their lean counterparts (47, 48). Interestingly, the relationship between BMI and blunted striatal response was particularly strong for those girls who possessed one at least one A1 allele of the *Taq*IA restriction fragment length polymorphism. Since positron emission tomography and post-mortem studies show that

the presence of this allele is associated with a 30-40% decrease in D2 receptors compared to those with the A2/A2 allele (49-51) we suggested that the blunted BOLD response may reflect alterations in the dopamine system. One important caveat is that neither the blunted BOLD response we observed, nor the reduced receptor availability observed by Wang and colleagues (46), provide insight into dopamine neurotransmission. It is entirely possible that fewer receptors result from a receptor down-regulation secondary to increased dopamine signaling and that the reduced BOLD response reflects neural events other than those associated with dopamine signaling. In addition, it is not clear how these blunted responses relate to perception. In humans food liking can be assessed by asking subjects to rate how pleasant a food is or how much they like certain foods. Although this may seem straightforward, it is now clear that the use of improper scales to compare food liking in lean vs. overweight individuals has lead to invalid data and much inconsistency in the literature (52). It therefore remains to be determined whether the pleasure associated with food is enhanced, decreased or unchanged in obese individuals. Whether or not whether the these effects observed in the dorsal striatum represent increased or decreased dopamine signaling and or experienced pleasure, they do predict future weight gain. Therefore future work aimed at elucidating the mechanism of the response, determining whether the response correlates with perceptual and behavioral measures of food reward, and determining whether it predicts conversion from lean to overweight is justified and needed. Further, even if the effect does represent an adaptation it would be important to determine if the adaptation confers further risk for overeating. It will also be important to reconcile these observations of blunted striatal response during food consumption with reports of increased dorsal striatal response to food cues in obese individuals (27,53).

Finally, several studies have reported heightened responses to food cues and/or food receipt in the insula, overlying operculum (27,48,53,54) and orbitofrontal cortex (OFC) of overweight vs. lean individuals (27,53). Del Parigi and colleagues found that the anterior dorsal insula (as well as the hippocampus) remain abnormally responsive in post-obese individuals scanned at rest following consumption of a liquid meal (55), possibly indicating a role for processing within these regions to play a role in susceptibility to overeat. The insula, operculum and OFC are regions of the brain that represent the sensory components of food, such as taste, flavor and oral texture (8,56-58), as well as enteroception (59), hunger and insulin levels (60). Response in insula, operculum and OFC to food consumption or exposure to food cues has been shown to be modulated by satiety (17,18,22,23,61), indicating that homeostatic and hedonic signals are integrated in these regions. In addition, a recent report by Batterham and colleagues showed that while neural response in the hypothalamus predicts feeding in hungry individuals, following administration of PYY, which mimics the sated state, it is response in the OFC that predicts feeding (62). This suggests that, like the amygdala, processing in the OFC can over-ride internal signals to promote feeding. It is therefore relatively straightforward to imagine how basic differences in sensory coding of food may lead to a predisposition to overeat.

In summary, there are several candidate mechanisms by which individual differences in the neurophysiology of reward may promote overeating. An important consideration for future work will be that differences may either reflect neural adaptations which result from the physiological and metabolic changes that accompany obesity or the neural substrates of stable behavioral traits whose persistence leads to obesity. Teasing apart these differences represents an important future direction. Another important consideration will be including likely moderating factors, such as phenotype and genotype in study design as well as drawing blood from subjects to begin to understand how peripheral signals such as leptin and ghrelin interact with reward networks at the level of the BOLD response.

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