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Interoceptive Contributions to Healthy Eating and Obesity

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Abstract

Obesity results from persistent failure by the brain to balance food intake with energy needs, resulting in a state of chronic energy surplus. Although there are many factors that predispose individuals to weight gain and obesity, the current review focuses on two ways eating behavior may be influenced by sensitivity to interoceptive signals of hunger, satiety, and metabolic energy reserves. First, obesity may be related to hypersensitivity to interoceptive signals of hunger, leading to positive alliesthesia for food cues that undermine attempts to change unhealthy eating behaviors. Second, overeating and obesity may arise from an inability to accurately detect interoceptive signals of satiety and positive energy balance. The findings reviewed herein demonstrate that obesity may be related to altered interoception, and warrant the continued development of novel obesity interventions aimed at promoting interoceptive awareness.

Keywords

Interoception; eating; insula; obesity

Worldwide, over 1 billion people are overweight, and more than 400 million are obese [1]. As a result, the World Health Organization ranks obesity as the most serious health issue facing the developed world (WHO, 2000). In many countries, public health systems are struggling to deal with the physical and psychological consequences of obesity and its concomitant illnesses, such as metabolic syndrome [2], sleep disorders [3], depression [4,5], diabetes [6], and heart disease [7]. The United States spends nearly \$150 billion per year in direct health care costs related to obesity [8]. These staggering statistics reflect the fact that hundreds of millions of individuals affected by obesity have spent a significant period of time in a state of chronic energy surplus, suggesting that their brains have at some point in time failed to accurately balance food intake with their actual energy needs. Here we will focus on a relatively under-studied contributor to this imbalance: how eating behavior is

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influenced by the perception and integration of largely vagal afferent signals conveying information to the brain about the physiological state of the body, a faculty otherwise known as interoception [9–11].

Traditionally, neuroscientists interested in appetite and eating have focused primarily on the role of endocrine energy-signaling molecules that travel from the periphery to the brain via the circulatory system, cross the blood brain barrier, and bind to receptors in the hypothalamus and other subcortical structures. Two particularly well-studied molecules are ghrelin and leptin [12,13]. These molecules are secreted in the periphery in response to fluctuations in energy states and act on neurons in the hypothalamus to affect appetite. Ghrelin, which is secreted by cells in the gastric mucosa, stimulates neurons that express orexigenic peptides and inhibits those that express anorexigenic peptides, leading to increased appetite. Leptin, in contrast, is secreted by adipose tissue and binds to receptors that express anorexigenic neuropeptides and inhibits neurons that express orexigenic peptides, thereby inhibiting food intake and promoting weight loss. Leptin, ghrelin, and other circulating molecules (e.g., adiponectin, cholecystokinin, etc. [14]) that exert their effects primarily through the hypothalamus have not traditionally been conceptualized as ‘interoceptive’ signaling systems. Yet, they are biological pathways through which the body’s energy state is communicated to the brain, and aberrations in these pathways can lead to an inability to accurately detect and respond to signals of energy surplus and satiety, promoting non-homeostatic feeding, prolonged positive energy balance, obesity, and its consequences to health. Going forward, there may be value in conceptualizing failures of the central nervous system to sense energy-related signals from the peripheral body (e.g., central leptin resistance, [13]) as a type of interoceptive deficit.

The Neurocircuitry of Interoception

Hypothalamic signaling is certainly important to our understanding of the regulation of healthy eating and weight. Likewise, various brain networks, particularly the dopaminergic reward system [15], have been highlighted in obesity. The present review, however, is primarily concerned with a less extensively-studied influence on appetite and eating: how vagal-to-insula interoceptive signaling, and its integration with reward processes, is critical to maintaining healthy eating behaviors. Although recently greater attention has been paid to the role of extra-hypothalamic influences on appetite (e.g., [16]), interoception per se is rarely discussed in detail. This is surprising given that the nervous system’s wiring diagram reveals that many of the signals relevant to satiety and food intake travel via the vagus nerve from the stomach to the brain, terminating in a unique region of the cortex that subserves *both* monitoring the state of the body and the sense of taste [9,17,18]. Specifically, the primary interoceptive and gustatory cortices are co-located within a region of the dorsal posterior-to-mid insular cortex [19–22], which receives afferent projections from the vagus via the solitary nucleus, parabrachial nucleus, and the ventroposterior medial nucleus of the thalamus, the dedicated visceral and gustatory thalamic relay [23]. Activity in this region of the insula is observed in neuroimaging studies using gustatory stimulation [24], as well as various types of viscerosensation, including cardiovascular arousal [25,26], heartbeat-evoked response [27], gastric distension [28], bladder fullness [29], and vagal nerve stimulation [17].

Once interoceptive information reaches the insula, it is passed back and forth among neurons along the insula's horizontal axis in a process that ultimately results in elaborate and highly integrated representations of the state of the body. Although various models exist regarding the precise neural computations underlying this process of elaboration and integration [30], recent theoretical accounts such as the Embodied Predictive Interoception Coding (EPIC) model [10] have emphasized Bayesian predictive coding (also see [31,32]). According to the EPIC model, the granular/dysgranular region of the mid-insula compares ascending viscerosensory signals from the body with predictions about the body's interoceptive state, generated by agranular visceromotor cortices located primarily in the ventral anterior insula and cingulate gyrus. The differences between the predicted and received interoceptive signals are computed as prediction errors in the mid-to-posterior insula, and then returned to anterior agranular visceromotor cortices where they are used to update the computation of subsequent interoceptive predictions.

Importantly, the EPIC model's Bayesian predictive coding perspective asserts that interoception and homeostatic–allostatic control are unified within an integrated neural architecture centered around the insula and the agranular visceromotor cortices to which it is highly connected [10,33]. Using both past experiences (empirical prior probabilities in Bayesian terms) and prediction error signals received from the mid/posterior insula, agranular visceromotor circuitry estimates the body's upcoming autonomic, metabolic and immunological needs given the demands of the current context. These estimates then serve three purposes in the brain. First, they inform efferent visceromotor, endocrine, and immunological commands that execute the changes required to maintain homeostasis or return the body to homeostasis (i.e., allostasis). Second, they become interoceptive predictions sent to the viscerosensory cortex about the interoceptive signals it should soon receive. Third, they underlie signals sent to other brain networks that inform stimulus valuations that guide behaviors that will help meet the body's homeostatic needs. In short, based on the insula's connectivity and cytoarchitectonic structure, the EPIC model ascribes to the insula a role in both interoception and homeostatic regulation through allostasis.

Positive Alliesthesia: Interpreting the external world through the lens of the body

To understand how altered interoceptive sensitivity may predispose some individuals to obesity, we need to first understand interoception's role in a key eating-related phenomenon: positive alliesthesia for food cues. The ability to accurately sense the body's interoceptive state (e.g., glucose or insulin levels, visceral signals of fullness, etc.) enables us to quickly generate allostatic visceromotor and behavioral responses that re-establish homeostasis and ultimately promote health. One way by which our brains move from detecting interoceptive signals of falling energy stores in the body (e.g., hunger, weakness, etc.) to generating behaviors that address these signals (e.g., seeking food, eating) is by increasing the motivational salience of food cues. The increase in reward value of a stimulus based on its potential to move the body's physiological state toward homeostasis is often referred to as 'positive alliesthesia' [34]. At least two sets of computations in the brain are thought to underlie the process of positive alliesthesia. First, the physiological state of the body at a

given moment of energy need is compared with stored representations of the body at homeostasis. Second, the reward value is adjusted upward for substances that can move the body back toward homeostasis by reducing the difference between the actual and ideal body state. The EPIC model readily embodies these processes: the first through the computation of prediction error signals by the mid/posterior insula, and the second through the transmission of these signals to the wider brain, particularly the agranular anterior insula and the numerous reward valuation and action planning regions to which it is connected [35].

The insula's role in positive alliesthesia is well known in the addiction literature. For example, in a study on nicotine withdrawal in individuals addicted to cigarettes, Avery et al (2016) found that interoceptive activity in the dorsal mid-insula predicts the increase in hedonic ratings for cigarette cues during smoking withdrawal [36]. Likewise, participants in another study who underwent seven hours without drinking liquid exhibited thirst that was associated with increased activity in the insula in response to images of beverages [37]. Similar findings are observed for food cues. Numerous brain imaging studies have now demonstrated that fasting and hunger result in potentiated activity to food stimuli within the insula and regions implicated in reward, motivation, and attention [38–43]. For example, Stice and colleagues showed that calorie deprivation is related to greater reward valuation of palatable food pictures and activation in the OFC, and that left mid-insula activation in response to milkshake was positively correlated with the number of hours spent fasting [44]. This finding may reflect the insula's role in detecting energy needs, as Simmons and colleagues demonstrated that circulating levels of peripheral plasma blood glucose modulates the response to food (but not non-food) pictures in the left dorsal-mid insula [45]. The fact that this effect was not correlated with participants' subjective hunger ratings, and because the insula has connections through the thalamus to one of the primary central nervous system sites for peripheral glucodetection located in the nucleus of the solitary tract [46], strongly suggests that the insula is in fact sensitive to energy availability.

Page and colleagues (2011) also demonstrated that peripheral glucose modulates the neural response to food cues [47]. In this elegant study, the authors demonstrated that hypoglycemia following insulin infusion was associated with increased activation of the striatum and insula in response to high-calorie food cues, thereby providing evidence that these regions underlie positive alliesthesia for foods most likely to quickly restore glucose levels [47] (for a related finding with insula resting-state functional connectivity, see [48]). A similar effect, but in the expected *opposite* direction, was reported by Kroemer and colleagues who used an oral glucose tolerance paradigm to demonstrate that increases in plasma insulin following glucose administration are associated with *decreased* responses to food cues in a number of brain regions, including the bilateral insula and OFC [49].

Interoceptive hypersensitivity may predispose some individuals to obesity

Extrapolating from the findings described above, one can speculate that obesity may be associated with *hypersensitivity* to signals of hunger, resulting in increased positive alliesthesia for food cues. For example, in healthy weight adults, fasting leads to increased insula activity and reward circuitry response to food cues, particularly those associated with high-energy foods (e.g., high-fat, high-sugar foods), thereby motivating food consumption

and undermining attempts to reduce intake [41]. Likewise, Page and colleagues demonstrated that obese adults exhibit greater activation of the bilateral insula, hypothalamus, striatum, substantia nigra and ventral tegmental area during hypoglycemia, a state that mimics the core metabolic feature associated with fasting [47].

There is a very pragmatic reason why it is important to assess whether at least a subset of obese adults experience hypersensitivity to interoceptive signals of hunger. In principle, hypersensitivity to the physiological effects of deprivation, and the resulting experience of heightened positive alliesthesia, should work against an individual's efforts to abstain from behaviors that are unhealthy. This has been particularly well documented in the drug addiction literature. For example, in the study of positive alliesthesia for nicotine cues described earlier, Avery et al (2016) found that activity in the mid-insula mediated the relationship between smoking abstinence and increased reward for cigarette cues, providing support for the integral role of interoceptive regions in positive alliesthesia following a reduction in a rewarding but unhealthy behavior [36]. As with nicotine and drugs of abuse, hypersensitivity to internal signals associated with hunger may contribute to the experience of positive alliesthesia for food cues, thereby undermining attempts to lose weight. Importantly, the converse may also be true. Simmons and colleagues observed that obese adults experiencing increased appetite during a major depressive episode rated food cues as more hedonically pleasing and exhibited greater activity in reward neurocircuitry in response to food cues [50]. Critically, however, it was the activity of the dorsal mid insula (bilaterally), and not the brain's reward circuitry, that was correlated with the subjects' hedonic ratings for foods. Those obese depressed individuals with increased appetite that exhibited the highest hedonic ratings for foods exhibited the lowest dorsal mid-insula activity. This inverse association suggests that greater processing of interoceptive signals about the state of the body (indexed by increased activity of the mid-insula) can in some cases act as a brake on food anticipation in those with overactive food reward signals (indexed by increased activity of reward neurocircuitry).

The findings relating mid-insula activity to appetite change in depression point toward the wider possibility that interoception serves as a critical link between food and mood. Although there exists a large literature demonstrating that interoceptive sensitivity to visceral signals can profoundly influence emotion (for review, see [51]), it is certainly not the case that visceral interoception exclusively mediates the relationship between homeostatic energy state and mood. For example, when glucose levels drop, the ensuing release of Neuropeptide Y not only alters energy metabolism, but also promotes angry aggression [52,53], which may partially underlie the relationship between hunger and anger (a.k.a. the experience of being "hangry"). In this state, interoceptive awareness of deviations from energy homeostasis can be a critical part in the recruitment of brain regions that support emotion regulation, thereby minimizing the social consequences of one's anger.

Importantly, however, interoceptive awareness of deviations from homeostasis may not only help to *control* emotional responses to these deviations, they may also contribute meaningfully to how these deviations are *experienced* as emotions. Drawing from Constructionist accounts of emotion (e.g., [54,55]), we can propose that interoception not only turns the physiological state of having low blood sugar into the cognitive experience of

“hunger”, but also provides the human conceptual system with information about the body’s somatic context, thereby influencing the construction of specific hunger-related emotional states. Because of this, the emotional response to *hunger* can be conceptualized in different ways (e.g., as either a lack of food, or a sign of successful dieting), and different energy-related interoceptive states can be conceptualized in the same way (e.g., lethargy can be attributed to either low blood sugar or lack of rest) (see[56]). This could have important clinical implications. Depression with increased appetite is associated with systemic metabolic and immune abnormalities [57–59] that likely influence energy homeostasis in profound ways. If the account described here is correct, a down-stream consequence of this physiological dysregulation may be that depression with increased appetite is associated with differences in the conceptual representation of emotion that could either contribute to depression, or serve as a point of intervention during psychotherapy. This may be a fruitful avenue for future studies in clinical neuroscience.

Interoceptive insensitivity as a path to overeating

If, as described in the previous section *hypersensitivity* to interoceptive signals of hunger might predispose overeating, it seems reasonable that *insensitivity* to interoceptive signals of satiety might also have the same effect. Over a half-century ago Schachter suggested that obese individuals might be relatively *less* sensitive to interoceptive signals of satiety than to exteroceptive food cues (e.g., seeing appetizing food) [60]. In a classic study supporting this contention, Stunkard and colleagues asked lean and obese women to rate their fullness while the researchers inflated balloons in the women’s stomachs [61]. The researchers observed a strong positive correlation between fullness ratings and balloon inflation-related stomach contractions in the lean women. In the obese women, the correlations were nearly zero, suggesting interoceptive insensitivity to signals of fullness. Recent neuroimaging results provide some support for this earlier finding, with amygdala and insula hemodynamic activity during mechanical distension of the stomach being negatively correlated with BMI [62]. Given the insula’s role in interoceptive sensation of stomach distension, this finding is highly consistent with the hypothesis that obesity may be associated with insensitivity to satiety signals. Likewise, there is growing evidence that obese adults may not exhibit typical satiety-related changes in brain activity following a meal (for meta-analyses, see [63,64]). Compared to lean subjects, obese adults fail to exhibit the expected drop in mid-insula activity to food cues following a meal, and this effect may be particularly pronounced in response to high-calorie foods [65]. This finding may indicate that obese adults are less sensitive to interoceptive signals of satiety that are presumably represented in the insula.

Studies implementing behavioral assessments of interoceptive channels not directly related to eating also suggest a relationship between interoceptive insensitivity and obesity, though these findings have been somewhat inconsistent. Using a heartbeat counting paradigm, Herbert and Pollatos (2014) compared cardiac interoceptive sensitivity as measured by a heartbeat counting task in 75 overweight and obese young adults and 75 age- and sex-matched healthy weight adults [66]. They observed that normal weight participants exhibited better heartbeat interoceptive sensitivity as compared to overweight and obese participants, and that the overweight and obese participants’ BMI was negatively correlated with interoceptive sensitivity. A separate study from this same research group using the same task

failed to observe a relationship between heartbeat interoception and BMI in children [67]. These mixed findings should be interpreted cautiously, as the validity of the heartbeat counting task as a measure of interoceptive sensitivity has recently come into question [68]. However, a negative relationship between interoceptive sensitivity and weight has also been observed in studies that implement other behavioral measures of interoception, such as the heartbeat detection task [69]. For a review of behavioral evidence for individual differences in interoceptive sensitivity to hunger and satiety, see [70].

Conclusion

The findings described above suggest at least two models wherein altered interoceptive sensitivity may predispose some individuals to unhealthy eating patterns: (1) obesity may be associated with *hypersensitivity* to interoceptive signals of hunger, resulting in increased positive alliesthesia and incentive salience for food cues, and (2) obesity may be associated with *insensitivity* to interoceptive signals of satiety. Importantly, these accounts are not mutually exclusive, even within an individual, and both find evidence in the literature.

A great deal of attention has been paid to the fact that obesity is associated with abnormal reward-related responses to food cues (for review see [71]). Although clearly this phenomenon is due in part to altered metabolic signaling via the hypothalamus [13] and altered activity in the dopaminergic system [15], the role of interoception, and the insula in particular, has received relatively less attention in the study of obesity. Effective interoception allows behaviors that are sensitive to the body's metabolic context, thereby maintaining homeostasis and ultimately promoting health. Going forward, researchers should explore whether interventions that improve interoception can promote eating behaviors that better match the body's energy needs. Indeed, recent functional neuroimaging evidence indicates that successful weight loss in adolescents following behavioral interventions (e.g., behavioral therapy, physical activity, and dietary counseling) are associated with increased insula activity [72], and increased post-meal resting-state functional connectivity between the insula and a region of the precuneus that serves as a hub within the brain's default mode network [73]. This is interesting in light of two recent developments in the treatment of obesity. First, there is a growing literature demonstrating that mindfulness-based interventions, many of which stress increased attention to interoceptive information from the body, are an effective tool for promoting healthier eating behaviors [74–76]. Second, the Food and Drug Administration has recently approved the use of vagal nerve stimulation, which delays gastric emptying and promotes fullness and satiety, as a treatment for obesity [77]. Taken together, these findings suggest that mindfulness-based interventions for overeating or vagal nerve stimulation could be most effective for those individuals who exhibit abnormal interoceptive sensitivity or insula activity during pre-treatment interoceptive tasks. These findings, and the growing recognition of the roles played by interoception in eating behavior, offer the hope of new intervention approaches that may address the crushing personal and public health burden of obesity.

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Highlights

1. A range of interoceptive processes are thought to affect eating and obesity.
2. Interoceptive hypersensitivity may undermine attempts to reduce unhealthy eating.
3. Altered interoception of satiety signals may contribute to obesity.
4. Interventions informed by interoceptive neurocircuitry may promote healthy eating.