Brain-based Etiology of Weight Regulation

Kyle S. Burger¹, Grace E. Shearrer², Abigail J. Sanders¹

¹Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill NC

²Department of Nutrition, University of Texas, Austin, TX

Address correspondence:

Kyle S. Burger
2204 McGavran-Greenberg Hall
CB 7461
Chapel Hill, NC 27599
Phone: 919-843-9933
email: kyle_burger@unc.edu

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ABSTRACT

Caloric intake and energy balance are highly regulated to maintain metabolic homeostasis and weight. However, hedonic motivated food intake, in particular consumption of highly rewarding foods, may act to override hemostatic signaling and contribute to overconsumption, weight gain and obesity. Here, we review human neuroimaging literature that has delivered valuable insight into the neural correlates of

hedonic motivated ingestive behavior, weight gain, weight loss and metabolic status. Our primary focus is the brain regions that are thought to encode aspects of food hedonics, gustatory and somatosensory processing, and executive functioning. Further, we discuss the variability of regional brain response as a function of obesity, weight gain, behavioral and surgical weight loss, as well as in type 2 diabetes.

INTRODUCTION

The determinants of ingestive behavior and weight regulation are frequently thought to involve homeostatic, hedonic, and somatosensory systems, which interact with the external environment to influence food intake and ultimately metabolic status (1,2). Homeostatic systems act to maintain energy balance and weight, primarily operating through appetitive peptide signaling (e.g., leptin, ghrelin, insulin, GLP-1) that acts on neural circuitry both directly and via the vagal nerve and to influence neuropeptides (e.g., neuropeptide Y, melanocortin-4 receptor agonist, cocaine amphetamine related transcript, agouti related peptide) in the hypothalamus. Somatosensory and gustatory brain regions (oral somatosensory cortex, anterior insula/frontal operculum [AI/FO]) are highly involved with aspects of taste response during food intake (3,4). Hedonic systems (pleasure/reward) modulate the homeostatic and somatosensory systems, with research indicating that the hedonic system can “override” the homeostatic need to eat (5), possibly contributing to excess food intake and weight gain. Dopamine and the dopamine 2 receptor (D2) are the cellular messenger and receptor encoding reward/pleasure in the

well-developed mesocorticolimbic circuitry (e.g., dorsal/ventral striatum, periaqueductal grey [PAG], medial orbitofrontal cortex [mOFC], ventral pallidum, amygdala). Mesocorticolimbic circuitry interacts with brain regions associated with executive functioning (e.g., dorsolateral prefrontal cortex [dlPFC], ventral medial prefrontal cortex [vmPFC]) to guide behavioral actions and ultimately food choice and intake. Unlike other hedonically motivated behaviors (e.g., substance use, sex, thrill-seeking, gambling) where the hedonic and executive functioning circuitries are primarily guiding behavior, there is a physiological need for food intake controlled by highly regulated homeostatic signaling (6). A summary of key brain regions that have been previously implicated in control of hedonically motivated food intake can be seen in **Table 1**.

Here, we review human neuroimaging literature that has delivered valuable insight into the neural correlates of ingestive behavior and weight regulation and metabolic status. As a framework, a working etiological model of many of the proposed psychological processes associated with the perpetuation of hedonically motivated is presented in **Fig 1A**. This is complemented by interplay with some of the metabolic mechanisms presented in **Fig 1B**. In this brief review, we aim to highlight brain and key metabolic responses associated with weight gain, obesity, type 2 diabetes (T2D), and weight loss. More mechanistic reviews of neural regulation of hedonically-motivated food intake and the neural pattern of hedonics in general can be seen in previous publications (7,8).

Relation of Brain Response to Food Stimuli, Weight Gain, & Obesity

Differential brain responses seen in obesity compared to healthy-weight

One of the most replicated findings in the neuroimaging of obesity is the elevated neural response to images of palatable and energy-dense foods seen in obese versus lean humans. Overweight/obese individuals consistently show significantly greater response in the striatum, insula, medial OFC, and amygdala (9–16). Similarly, during cue-elicited anticipation of receipt of palatable food, obese individuals also show greater response in gustatory and somatosensory brain regions (postcentral gyrus, rolandic operculum, AI/FO) and regions associated with visual processing and attention (visual and anterior cingulate cortices), the encoding of stimulus salience (precuneus (13,17,18)). In seemingly contrast aforementioned to the increased response to food cues and anticipatory stimuli, obese individuals consistently show less striatal response to receipt of palatable food relative to their lean counterparts (17,19–22). Collectively, these data highlight the dynamic process that is ingestive behavior, where obese and overweight individuals show an elevated striatal response to anticipatory cues (e.g., images, predictive cues) and decreased striatal response during consumption. However, these data and theories inherently presume a static neural response despite the high likelihood of neuroadaptations associated with repeated consumption of rewarding foods and recurring exposure to the associated food cues, as well as the known altered neuroendocrine functioning that is associated with obesity.

Predictors of and neuroadaptations associated with weight gain

Using neural response to food receipt and food cues in prospective studies allows for the examination of baseline brain response as predictors of future behavior and/or health outcomes (23). This ability could be used to identify previously unseen brain-based risk factors that could be targeted for prevention efforts. For example, ventral striatum and anterior cingulate response to appetizing food images at baseline predicted future weight gain over a 6-month follow-up (24). Further, individuals who showed greater activity in the OFC in response to a cue predicting palatable food gained more weight over one year (25). Concordantly, striatum, ventral pallidum and midbrain response to a milkshake receipt was positively related to weight gain at one-year follow-up (18) and, when sated, amygdala response to milkshake receipt predicted weight gain (26). Together, these data indicate that those individuals with a greater response in regions thought to encode aspects of reward are at higher risk for weight gain. Essentially, greater reward response to a cue predicted weight gain risk.

Additional evidence indicates genetics may influence this response pattern. Several genes influence dopamine functioning, including those that affect dopamine receptors, transport, and breakdown; research has indicated that variants of Taq1A polymorphism of the DRD2 gene has a large impact of on dopaminergic functioning. The Taq1A polymorphism has three allelic variants: A1/A1, A1/A2, & A2/A2, where individuals with genotypes containing one or two copies of the A1 allele have 30-40% fewer D2 receptors and compromised brain dopamine signaling than those without an A1 allele. Among individuals with an A1 polymorphism of the Taq1A allele, decreased dorsal striatal

response to milkshake receipt predicted weight gain at one-year follow-up (19) and increased body fat at three-year follow-up (27). Whereas among those without an A1 allele increased dorsal striatal response to milkshake receipt predicted weight gain at one-year follow-up (19).

Few repeated-measures fMRI studies exist that are able to map the within-subject changes in brain response as a function of weight gain. Of those available, change in BMI over a 6-month period was positively related to activity in the insula and visual cortex activity during exposure of appetizing food images, relative to baseline scans (28). Interestingly, weight gain over a 6 month period was associated with reduced striatal response to palatable food receipt (29). These data suggested, that weight gain alters hedonic response to food stimuli. Specifically, response to palatable food cues and/or images increases, while, in contrast, the response during palatable food intake is decreased.

Relation of Brain Response to Food Stimuli and Type 2 Diabetes

The interplay between body composition and metabolic health is also associated with differential neural response to food images and receipt. The classic example of the relationship between weight status and metabolic health can be seen in type 2 diabetes patients. The central nervous system has been repeatedly shown to be insulin sensitive (30–33). Additionally, T2D in the brain highlights the interplay of homeostatic systems residing primarily in the hypothalamus and higher level reward networks. Page et al, demonstrated glucose ingestion reduced hypothalamic activation and functional connective hypothalamic-striatal networks (34), highlighting the relationship between homeostatic and hedonic

brain glucose action. A study examining the difference between lean and overweight adults' neural processing of low and high calorie food cues used an oral glucose tolerance test (OGTT) and a water control showed insulin impacts prefrontal activity in response to high calorie food cues (35). These results and others (30,32,33), suggest a potential cerebral insulin resistance culminating in reduced postprandial inhibitory control and overeating. Furthermore the same OGTT study highlighted that when viewing high calorie foods hypothalamic activation was inversely correlated with blood glucose similar to Page's findings above (35). These experiments highlights the importance of insulin and glucose status on homeostatic regulation and executive function.

Altered leptin is also seen in type 2 diabetes (36) and is known to influence food intake (37). Patients with insulin resistance also exhibit elevated leptin levels, independent of body composition (38). In a study with obese adolescences, higher endogenous leptin was associated with increased neural activation in the caudate, insula, and amygdala to high calorie food images (39). The increase in neural activation suggests obese, compared to lean, adolescents show an increased responsivity to food stimuli, while the elevated leptin may allude to leptin resistance in these subjects similar to the increased circulating insulin in insulin resistant and T2D patients (40). While causation cannot be stated from these studies, it does appear that leptin alters food related behavior and this may exacerbate type 2 diabetes or vice versa.

Additionally, GLP1 is a gut derived incretin known to increase post meal satiety. However in patients with T2D research shows reduced postprandial GLP1, potentially reducing satiation and further contributing to aberrant insulin secretion (41). Between obese subjects with and without T2D and lean controls, intravenous GLP1 agonist administration decreased desire to eat in the obese subjects with and without T2D. Additionally, the GLP1 agonist decreased response to food images in the caudate, insula, and OFC (42), illuminating the possibility that GLP1 plays an important role regulating insulin response and food intake.

A bulk of the neuroimaging research in T2D patients focuses on cognition and attention. In particular, this research has used resting state MR imaging (rsMRI), to visualize potential differences in control networks related to cognition and attention. Xia and colleagues have well documented differential brain connectivity networks between T2D patients and controls (43–45). T2D patients exhibited lower interhemispheric connectivity. In particular the middle temporal gyrus was inversely correlated with Trail making test-B (TMT-B) performance and homeostatic model assessment of insulin resistance (HOMA-IR) (45). Additional work showed disruption in attention-related brain networks and HbA1c status (44).

Relation of Brain response to Food Stimuli & Weight Loss

Neuroadaptations behavioral weight loss efforts

The effect of calorie restriction should, theoretically, create an energy imbalance that result in weight loss. However, for a majority of people, long term, sustainable weight loss via caloric restriction is highly improbable and generally ineffective (46,47). The neural patterning associated with weight loss and/or successful maintenance of reduced weight is poorly understood. Weight loss over a 6 month period has shown to alter the functional connectivity of the default mode network (DMN) of the brain 'at rest' particularly connections stemming from the precuneus. The precuneus is commonly associated with the salience of stimuli and has been associated to the preference of food (48). Additionally, there are neural mechanisms in place to defend against weight loss. Caloric restriction in mice produced increasing circulating ghrelin which was associated with increases of dopaminergic activity in the ventral tegmental area, resulting in increased reward value of food (49). Restrained eating, the intentional restriction of calories with the overall goal to lose weight (50), is related to subsequent weight gain in individuals and is positively correlated with reward expectation and attention to food (51,52). Self-reported restrained eating is positively correlated with brain regions associated with reward encoding (e.g., OFC), somatosensory and gustatory regions (e.g., postcentral gyrus, and anterior insula) and brain regions that encode visual processing and attention (e.g., lingual gyrus, cuneus, and inferior parietal lobule (53,54). Moreover, even unintentional caloric deprivation results in increased response in reward and attention related brain regions during exposure to food stimuli (55). These studies indicate that restrained eating, through an increase in reward encoding and attention to a food stimulus, thwarts

weight loss efforts.. In support of this notion, greater striatum and insula activity when viewing energy-dense foods at baseline was found to predict poorer outcome in a weight loss program over 9-month follow-up (56) suggesting that individuals with elevated responsivity to appetizing food cues in these regions are less likely to respond to a behavioral weight loss intervention.

Interestingly, there are emerging data indicating that physical activity may alter the brain's responses to food stimuli. For example, chronic exercise training was associated with attenuation in the response to food images in the insula and visual processing regions (28), the OFC (encoding reward), and increased response in the dlPFC (executive functioning; (57)). Acute bouts of exercise increased the neural response in reward and gustatory regions to low-calorie food relative to high-calorie food (57) and exercise reduced the response to food cues vs. control cues in the putamen, and the insula and rolandic operculum (secondary somatosensory cortex) (58). In sum, chronic and/or short-term exercise may attenuate many networks in the brain that drive excess food intake. If true, this indicates that exercise has dual benefits in promoting energy balance and a healthy weight; directly increasing energy used and indirectly decreasing energy intake. While promising, these data are few, and warrant further investigation.

Neuroadaptations to surgical weight loss

Increasingly, surgical procedures have become an attractive alternative to dieting for sustained weight loss, in particular for morbidly obese individuals. Currently, three procedures dominate the bariatric

surgery environment: Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), and sleeve gastrectomy (SG). With surgical weight loss comes expedited weight loss and amelioration of obesity co-morbidities (e.g., cardiovascular disease and type 2 diabetes), as well as profound alterations in food preference. The mechanism behind the resolution of co-morbidities and food preference is still largely unknown. Current research focuses on the possibility of hormonal alterations due to the surgery itself or to weight loss, dopaminergic differences, and/or learned aversion to explain the change in food preference.

RYGB is considered the “gold standard” for both bariatric surgery and weight loss for severe obesity ($\text{BMI} \geq 40$) (59), and current studies report it improves weight loss better than LAGB or SG (60). Miras and le Roux have well documented the curious effect of RYGB on taste preference post operation (61). Post RYGB subjects significantly preferred low fat and low sugar foods compared to pre operation (61). However, the same subjects experienced heightened sweet taste acuity (61). Functional neuroimaging of post operational subjects revealed a significant reduction in mesocorticolimbic circuitry, the lentiform nucleus, putamen, middle and superior frontal gyri, activation one month after surgery in response to a food stimuli (62). Additionally, this reduction was more pronounced in response to images of high-calorie foods versus low-calorie foods (63). The decreased activation in the mesocorticolimbic circuitry predicted reductions in desire to eat (63). RYGB subjects demonstrated a reduction in regions thought to encode aspects of reward when compared to pre-operational scans as well as LAGB subjects (64).

Specifically, images of high calorie foods were rated less appetizing and elicited less activation in the OFC, putamen, caudate, nucleus accumbens, hippocampus, and cingulate and paracingulate gyri between the two surgery groups, however no difference was seen when looking at low calorie foods (64).

Although it is generally accepted that RYGB results in changes in food preference, and that this is reflected in fMRI studies, the mechanism behind the gut brain interaction is still largely unknown. The RYGB procedure has been hypothesized to increase the nutrient sensing ability of intestinal L-cells, responsible for the secretion of the satiety peptide hormones GLP1 and peptide tyrosine tyrosine (PYY) (65), suggesting that a potential increase in these satiety hormones mediates the preference change from high to lower calorie foods. This idea has been supported in type 2 diabetes research showing the GLP1 analogue, liraglutide, reduced preference of fat containing foods in type 2 diabetic men (66). However, one should note, that GLP1 and PYY are quickly metabolized in circulation, unlike the longer lasting liraglutide. An alternate hypothesis suggests that the physical distention of the stomach via the vagal nerve stimulates GLP1 secretion within the central nervous system resulting in increased satiety directly (67).

de Weijer suggests that decreases (68) in D2 availability after RYGB was not related to fat mass alone (69). Rather, insulin and dopamine interact to alter D2 availability. Elsewhere, insulin sensitivity has been shown to be negatively correlated with D2 binding potential in obese versus lean females

(70), and specifically reduced insulin sensitivity has been associated with dopamine depletion in the ventral striatum (71). This is particularly interesting considering that post RYGB insulin sensitivity was improved in as little as six days post operation (72), as well as suggests an important role for dopamine on insulin sensitivity and vice versa.

In a study comparing RYGB to LAGB, the LAGB group also did not rate high calorie foods as less appetizing as low calorie and also did not show the same decrease in activation as the RYGB group (64). The RYGB group did exhibit higher GLP1 compared to the LAGB group after a meal (64). Subjects post LAGB experienced fewer instances of dumping syndrome compared to subjects post RYGB (64). Overall, RYGB have greater weight loss outcomes compared to their LAGB counterparts, and this could be a result of higher GLP1 concentrations or an increase in learned aversion due to dumping syndrome, both of which also could explain the different ratings of high calorie foods. When compared to non-surgical dieters with similar weight loss, LAGB subjects exhibited reduced food related motivation and reward activation to pictures of food, while simultaneously showing increased cognitive restraint (73,74).

Conclusions

Considerable advances have been made in the understanding of the complex neural system that plays a critical role in eating behavior and weight regulation. However, to date, these advances in understanding the neural etiology of weight regulation have relied heavily on a reductionist approach

frequently focusing on interpretation of data from studies as if the systems discussed here act in isolation, when there is a interplay among hormonal signaling, neural response and genetics that all act to guide behavior. The neural response patterns associated with hedonically motivated food intake frequently draw parallels to substance use/abuse. In particular, repeated intake of palatable food or drug use results in similar reductions in the responsiveness of brain mesocorticolimbic systems (see (7) for review). However, independent of the notion of food/sugar addiction, the regulation of food intake is exceedingly more complex from both an etiological and intervention standpoint as there is physiological need for calories for survival and multiple hedonic and homeostatic systems in place to insure these needs are met.

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Compliance with Ethics Guidelines

Conflict of Interest

Kyle S. Burger, Grace E. Shearrer, and Abigail J. Sanders declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Table 1. A network of key brain regions associated with the control of hedonically motivated food intake¹

Brain region	Anatomical or functionally defined²	Generalized role in the control of food intake
Hypothalamus	Anatomical	Homeostatic control/intersection of metabolic signaling
Amygdala	Anatomical	Hedonic processing
Dorsal anterior cingulate cortex (dACC)	Functional	Hedonic processing/visual attention
Dorsal Striatum	Functional	Hedonic processing
Medial orbitofrontal cortex (mOFC)	Functional	Hedonic processing
Middle orbitofrontal cortex (midOFC)	Functional	Hedonic processing
Nucleus accumbens (NAcc) / Ventral striatum	Functional	Hedonic processing
Periaqueductal grey (PAG)	Anatomical	Hedonic processing
Ventral pallidum (VP)	Functional	Hedonic processing
Subgenual anterior cingulate cortex (sACC)	Functional	Hedonic processing
Substantia nigra (SN) / Ventral tegmental area (VTA)	Anatomical	Hedonic processing
Habenula	Anatomical	Inversely related to food hedonics
Anterior insula/frontal operculum (AI/FO)	Functional	Taste and gustatory, hedonic processing

Oral somatosensory cortex	Functional	Oral somatosensory processing
Posterior cingulate cortex / Precuneus	Functional/Anatomical	Perception of hedonic value independent of valance
Dorsolateral prefrontal cortex (dlPFC)	Functional	Executive functioning
Lateral orbitofrontal cortex (IOFC)	Functional	Executive functioning
Ventromedial prefrontal cortex (vmPFC)	Functional	Executive functioning

¹Contact the author for individual masks of these regions for use in neuroimaging analyses.

²Evidence indicates that many anatomical regions may have sub-regions that are functionally defined, those functionally defined here are currently represented in the human neuroimaging/food hedonic literature.

Figure 1. Display of **A)** psychological and **B)** metabolic processes associated hedonically motivated food intake.

Figure 1.

A)

B)