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Brain–gut–microbiome interactions in obesity and food addiction

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Abstract

Normal eating behavior is coordinated by the tightly regulated balance between intestinal and extra-intestinal homeostatic and hedonic mechanisms. By contrast, food addiction represents a complex, maladaptive eating behavior that reflects alterations in brain–gut–microbiome (BGM) interactions and a shift of this balance towards hedonic mechanisms. Each component of the BGM axis has been implicated in the development of food addiction, with both brain to gut and gut to brain signaling playing a role. Early life influences can prime the infant gut microbiome and brain for food addiction, which might be further reinforced by increased antibiotic usage and dietary patterns throughout adulthood. The ubiquitous availability and marketing of inexpensive, highly palatable and calorie dense food can further shift this balance towards hedonic eating through both central (disruptions in dopaminergic signaling) and intestinal (vagal afferent function, metabolic toxaemia, systemic immune activation, changes to gut microbiome and metabolome) mechanisms. In this Review, we propose a systems biological model of BGM interactions, which incorporates published reports on food addiction, and provides novel insights into treatment targets aimed at each level of the BGM axis.

Introduction

The obesity epidemic continues to be a major public health problem both in the USA and globally.[1,2] Obesity is defined as a body mass index (BMI) ≥30 kg/m^2 and a BMI ≥40 kg/m^2 is considered extreme obesity, with overweight classified as 25–29.9 kg/m.[1,2] The prevalence of obesity worldwide has tripled since 1975, with ~39% of the world's adult population being overweight and 13% being obese in 2016.[2] In the USA alone, the number of individuals with obesity continues to dramatically increase, with >35% of individuals

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Competing interests

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being overweight, >37% obese and 8% morbidly obese.[2,3] Obesity is the biggest driver of preventable chronic diseases and healthcare costs in the USA, with current cost estimates ranging from $147–210 billion per year.[4] Despite the magnitude of the problem and the associated healthcare costs, drug development efforts have largely failed and proposed treatments have had disappointing outcomes, with only modest reductions and frequent weight regain after successful weight loss.[4,5]

Obesity has a complex and multifactorial aetiology and the limited progress in obesity treatments can in large part be attributed to the failure to apply a systems biology-based approach to understand its pathophysiology and to develop individualized strategies to achieve sustained weight loss and prevention[6,7] A growing body of largely preclinical studies support the concept of bidirectional signaling within the brain–gut–microbiome (BGM) axis in the pathophysiology of obesity, mediated by metabolic, endocrine, neural and immune system mediated mechanisms.[8] Signaling from the brain through the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis influences many gastrointestinal processes, including motility and transit,[9] fluid and mucus secretion,[9] immune activation, intestinal permeability,[10] relative gut microbial abundances,[11] as well gene expression patterns in certain pathogenic gut microorganisms.[12] Changes in the gut luminal environment can affect gut microbial community composition and function.[13,14] Conversely, the gut microbiota can communicate with the brain via hundreds of metabolites, [15-17] which are sensed by specialized cells in the gut, including enteroendocrine cells, enterochromaffin cells and primary or secondary afferent nerve endings. Sensing of bacterial metabolites by these cells results in neural signaling to the brain, interactions with gut-based immune cells leading to local and systemic immune activation, or the metabolite might achieve sufficient concentrations in the circulation to directly access brain circuits by crossing the blood–brain barrier.[18] Short-chain fatty acids (SCFAs), the main byproduct of microbial fermentation of dietary fiber, have emerged as key mediators of BGM signaling.[19] These saturated fatty acids can influence the central nervous system (CNS) through immune-,[20] endocrine-,[21] and vagal- pathways.[22]

The gut microbiome and bidirectional BGM interactions are programmed through influences during pregnancy and the first 1,000 days of life,[23] and are subject to multiple perturbations from within the body (including from metabolism, gut microbiota interactions and energy expenditure) and from the environment (for example, via food, stress and medications) throughout life (Figure. 1). Perturbations at any level of the BGM system, resulting in compromised inhibitory mechanisms that normally regulate food intake, can bias ingestive behaviors towards predominantly hedonic-driven eating beahviours, cravings and overeating[24-27]. An extensive literature exists on the homeostatic regulation of food intake and maintenance of body weight via interactions between hypothalamic nuclei and orexogenic and anorexogenic gut hormones, in addition to chemical signals derived from adipose tissue, in particular leptin.[28-30] However, it is ultimately the complex balance between gut-derived orexogenic (ghrelin, insulin) and anorexogenic signals (including cholecystokinin, neuropeptide Y (NPY) and glucagon-like peptide-1 (GLP1)), gut microbial metabolites (SCFAs and amino acid metabolites), stress mediators (corticotropin releasing factor (CRF)), and the motivational drive generated by the central reward system

(dopaminergic reward system) and prefrontal cortical inhibitory mechanisms that determine how much we eat.[31-33]

A particular type of eating behavior which has been referred to as food addiction, plays an important part in the pathophysiology of obesity.[34,35] Food addiction is the continued consumption of highly palatable foods even after energy requirements have been met and despite known negative physical and psychological consequences in response to uncontrolled food ingestion.[34,36] Similar to other forms of substance abuse, food addiction represents an addiction-like response to food (especially foods rich in sugar and fat) or the process of eating itself in susceptible individuals.[37,38]

Since it was first proposed by T. Randolph in 1956,[39] there has been an ongoing controversy over the term of food addiction,[40,41] despite strong arguments supporting shared underlying pathophysiology between drug and food addiction.[33,42] On a behavioral level, individuals with food addiction as identified by the Yale Food Addiction Scale (YFAS)[43] meet the diagnostic criteria for substance abuse disorder found in the Diagnostic and Statistical Manual of Mental Disorders[44], which involves loss of control over eating, excessive time or focus on food, neglect of other activities and continuation of the behavior despite known negative consequences.[45-47] An increasing number of research reports on the biological alterations in the extended reward network in both humans and rodents also point towards strong similarities in the mechanisms underlying substance use disorders and food addiction, including substantial commonalities between the neural substrates underlying the substance abuse and at least some forms of obesity that involve food addiction.[31-33] For example, the biological similarities between individuals with obesity with food addition and individuals with drug addiction include, but are not limited to, changes in the dopaminergic pathways within the reward system, and in cortical performance monitoring, both of which are involved in processes associated with reward sensitivity, motivation, interoceptive awareness, stress reactivity and self-control.[48-50] Despite these similarities, there are also clear differences. Although the development of predominantly hedonic driven eating behaviors involves food-induced alterations in multiple peripheral and central mechanisms of the BGM axis, drug addiction results from a direct effect of the drug on the brain.[51,52] In addition, in contrast to the nearly universal development of addiction upon exposure to a drug, food addiction as assessed by the YFAS score is present in only a subgroup of individuals with obesity.[46,53] On the basis of questionnaire-based surveys and by other methods of assessment, food addiction is present in 25–37% of individuals with obesity, reaching rates of up to 60% in those who are morbidly obese or in patients who undergo bariatric surgery.[36,38,54-60] Food addiction is also highly associated with eating disorders such as bulimia nervosa and binge eating disorder.[61,62]

Previous work on obesity and food addiction crosses over multiple fields of research: neuroscience, gastroenterology, microbiology, endocrinology, immunology and many others. For example, the gut microbiome, intestinal signaling, extraintestinal signaling (visual, olfactory, food memories), early life programming of food preferences and many other factors can contribute to food addiction. Here, we review and build on past work to create a systems-based BGM model of obesity and food addiction. Systems biology is an interdisciplinary field of study that focuses on complex interactions within multiple

biological systems, rather than focusing on individual mechanisms. One of the aims of systems biology is to model and discover emergent properties of cells, tissues and organisms functioning as a system rather than as individual parts. We believe that such an interdisciplinary, system-based approach is able to create a more nuanced understanding of food addiction, as shown in Figure 1. In this Review, we summarize the physiology of food addiction in obesity as it relates to alterations within the brain and the gut microbiome. We will introduce key factors that influence the BGM axis such as diet, antibiotics, early life adversity, food cues and psychological stress, during the prenatal and postnatal period, and during adulthood. This Review also discusses several therapies aimed at food addiction in individuals with obesity, including those targeted at the gut, the microbiome and the brain, and highlights limitations and areas for future research in the field.

Ingestive behaviour physiology

The role of the gut microbiome

Ingestive behavior represents a delicate balance between homeostatic and hedonic regulatory mechanisms in the CNS, orchestrated by a number of gut peptides, neuronal impulses, endocrine signals and countless other influences, including signals generated by the gut microbiota (Figure 1).

BGM interactions involving gut peptides that regulate ingestive behavior have been the most extensively studied. The gastric hormone ghrelin has an important role in producing hunger and craving,[63,64] perhaps through amplification of dopaminergic signaling mechanisms,[65] whereas the intestinal hormones GLP1[66] and peptide YY[67] trigger satiety and associated behavioral changes. Increased production of microbiota-derived SCFAs can stimulate enteroendocrine cells to release GLP1[68] and peptide YY[69], while decreasing the secretion of ghrelin.[70]

Insulin is another orexogenic hormone, as hyperinsulinaemia, regardless of plasma glucose levels, contributes to increased sensations of hunger and results in a heightened palatability of sucrose.[71] Animal evidence suggests that disruptions of microbial SCFA metabolism can promote insulin resistance and hyperinsulinaemia,[72] thereby potentially shifting the balance towards hedonic behaviors. For example, studies in mice have shown that increased production of acetate by an altered gut microbiota can lead to activation of the parasympathetic nervous system which in turn promotes increased glucose-stimulated insulin secretion and increased ghrelin secretion resulting in hyperphagia.[73]

Additionally, gut microbiota-derived secondary bile acids can regulate insulin sensitivity through signaling involving the nuclear farnesoid X receptor (FXR) and the G protein-coupled receptor TGR5 (also known as G-protein coupled bile acid receptor 1 GBAR1).[74] Activation of intestinal FXR in a mouse model induces microbial production of the secondary bile acid lithocholic acid, driving TGR5 signaling and triggering GLP1 secretion from enteroendocrine L-cells.[75] Exposure to oral broad-spectrum antibiotics (combination of ampicillin, vancomycin, neomycin sulfate, and metronidazole) successfully inhibited microbial lithocholic acid production and completely reversed improvements in insulin sensitivity.[75] In a single blind randomized controlled trial of 20 individuals with obesity,

administration of an oral antibiotic (vancomycin) for just 1 week resulted in reduced microbial diversity (mainly affecting Firmicutes), with an associated drop in secondary bile acids as well as in insulin sensitivity.[76]

An example of microbial regulation of food preferences has been shown in a study demonstrating that fruit flies fed a diet deficient in essential amino acids show preferential intake of amino acid-rich foods.[77] These preferences are, however, blunted by the presence of both *Acetobacter pomorum* and lactobacilli.[77] Of note, neither *Acetobacter pomorum* nor lactobacilli were capable of modulating food intake individually, suggesting that these microorganisms must work together to influence host behavior.[77] Although the mechanisms driving food seeking behaviors in this model remain unclear, microbial modulation of neuronal TOR signaling has been previously proposed as an important mediator of nutrient balance and growth in *Drosophila*.[78,79] In fruit flies exposed to a nutrient scarce environment, *Lactobacillus plantarum* can promote protein assimilation from the diet, resulting in increased production of branched-chain amino acids.[79] These amino acids activate central nervous system (CNS) TOR kinase activity, resulting in the release of insulin-like peptides.[79]

The role of the brain

Neuroimaging studies have improved our understanding of the role of the brain in ingestive behavior in both animals and more recently in humans, especially the interplay of various brain networks involved in homeostatic mechanisms versus food addiction (non-homeostatic).[50,80-82] The homeostatic component of food intake is comprised of hormonal regulators of hunger, satiety and adiposity levels.[83,84] The hypothalamus is the primary brain area within the homeostatic system that regulates food ingestion and energy balance, and hence is often referred to as the ‘satiety centre’ or ‘feeding centre’ of the brain.[85-87]

Normal ingestive behavior is under the control of the extended reward network, which includes brain regions from the core reward network such as the nucleus accumbens, ventral tagmental area or substantia nigra, and are regulated by cognitive network regions such are the prefrontal cortex.[88,89] The extended reward network is involved in the processing of rewarding stimuli and modulation of food-seeking behavior,[90,91] inhibitory control,[92] cognitive performance monitoring,[93,94] interoceptive and sensory awareness,[88,95,96] and integrating salient information to make decisions regarding food intake.[97-100] This processing includes brain regions concerned with interconnecting brain networks such as reward, salience, emotional regulation, the somatosensory system and cortical inhibition (prefrontal control) networks (Figure 2).[31,33,90,99] The salience network is responsible for monitoring the homeostatic state of the body to make adaptive adjustments to real or expected disturbances in homeostasis through autonomic nervous system, as well as behavioral responses.[98,101] In food addiction (as in substance abuse), the saliency of a specific type of reward (food or drug) becomes greater at the expense of other rewards.[32,48] The emotional regulation network is activated by stimuli threatening the homeostasis of the organism, and provides a rapid feedback inhibition of such activation via its connections with the salience network.[89,102,103] Advanced analytical techniques such as brain network metrics based on graph theory, which measure the underlying architecture and flow of

communication between brain regions and networks, and multivariate machine learning methods that predict obesity have been applied to phenotype hedonic ingestion-related brain signatures, with a focus on alterations in the extended reward network.[88,89,104-107]

Homeostatic versus hedonic systems

Homeostatic system.—The hypothalamus acts as a hub integrating information from the external environment, such as food availability and stress, and from the internal milieu of the host to meet real or perceived nutrient needs.[108,109] Lesions in the hypothalamus, in both humans and animals can lead to increases in appetite, food ingestion and weight gain.[110,111] Numerous studies have been directed at identifying the molecular mechanisms within the hypothalamus underlying these processes.[85,108,112] For example, animal models have demonstrated that brief electrical stimulation of nuclei within the hypothalamus can cause the increased expression of genes related to Agouti-related protein (AGRP)–NPY–γ-aminobutyric acid (GABA) signaling, which in turn can cause voracious food ingestion.[113,114] These targeted cells have, therefore, been referred to as ‘hunger neurons’.[86,115] The hypothalamus has close interactions with corticolimbic and medullary pontine regions integrating sensory information mediated by vagal afferents, affective state and cognitive modulation to generate appropriate motor responses and adaptive eating behaviors.[85]

Hedonic system.—Individuals with obesity and with food addiction are more likely than individuals who are lean or obese without food addiction to display a heightened motivation to eat highly palatable foods, consume more calories from fat and protein, and have at least 20% prevalence rates with comorbid conditions, such as depression, binge eating, and decreased quality of life functioning, beyond that observed with obesity alone.[116-119] The closely regulated balance between hedonic and homeostatic aspects of ingestive behavior can be altered when normal inhibitory regulation of the reward system is compromised via decreased modulation or connectivity, resulting in overconsumption of food. There are similarities between food addiction and other addictive behaviors, as both reflect an imbalance in responses within the brain’s extended reward system to stimuli from the environment.[33,120] In food addiction, such uncoupling can be the result of central as well as peripheral disturbances in brain–gut interactions, including diet-induced neuroplastic changes in the sensitivity of vagal afferent nerve terminals and of hypothalamic nuclei to satiety hormones,[121-123] emotional state, and easy access to highly processed and palatable foods that all modify the rewarding properties of food, thereby leading to overconsumption.[32,48] Both human and animal studies have shown that increased cravings and food addiction behaviors result in increased conditioning and motivation to seek these highly palatable foods, and these behaviors are based on alterations of regions within the extended reward network.[31,33,124,125]

Evidence also exists suggesting that, similar to other addiction like behaviors, food addiction is associated with a reduced response of the reward network.[126] For example, ingestion of rewarding foods or drugs leads to reduced dopamine signaling within the reward system in both individuals with obesity and those with drug addiction,[127] suggesting that a reduction in dopamine signaling (by both the reduced release of dopamine and the downregulation of dopamine receptors) might contribute to the overconsumption and increased cravings of the

drug of choice.[128-130] According to the dopamine deficiency hypothesis, reduced dopamine release in the striatum alters corticostriatal communication between the basal ganglia (core reward) and the extended reward system, resulting in compromised inhibition of connectivity in the reward regions.[131] Reduced cortical inhibition of reward regions is also associated with greater cravings and reduced disinhibition scores.[132-134]According to this theory, hypo-dopaminergic function also leads to reduced levels of subjective well-being, as it is linked to dysregulation of other neurotransmitters such as 5-HT, enkephalins and GABA.[131] To compensate for this dopamine deficiency, it has been suggested that affected individuals will engage in behaviors that stimulate the brain's production and utilization of dopamine, such as by the overconsumption of highly palatable and rewarding foods, [131,135,136] increasing the risk of developing food addiction and obesity.[137,138] Thus, a stronger stimulus (for example, increased food intake) is required to overcome the reduced responsiveness of the dopamine system, similar to mechanisms identified in disorders of addiction, and failure to achieve this goal is associated with food cravings and the engagement of the stress response.[31,32,48,139,140] Stress induced eating usually depends on a number of factors such as the length of the stress, type of stressor, type of foods available, especially if calorie dense and highly palatable, length of time exposed to the food, and satiety and hunger levels.[124] Studies have shown that during stress, increased cortisol levels could contribute to increased gluconeogenesis, an upregulation of corticotrophin releasing factor (CRF) in the amygdala and other limbic regions, and consequently the blunting of HPA axis function, which in turn leads to low dopamine and reward functioning commonly associated with food addiction.[125] Stress has also been associated with increases in ghrelin and cortisol and related increases in craving and intake of highly palatable foods, which were higher in those with obesity and overweight than lean individuals.[141] A study performed in obese rats demonstrates downregulation of striatal dopamine D2 receptors compared to lean rats, similar to what has been shown in previous studies of humans addicted to drugs.[142,143] Furthermore, D2 receptor knock down mice rapidly develop compulsive-like food seeking behaviors when high-fat food is readily available.[142]

Even though dopamine has been the most thoroughly investigated signaling system in addictive behaviors, several neurotransmitters other than dopamine and neuropeptides are involved both in the homeostatic regulation of food intake (including orexin, leptin and ghrelin, corticotropin releasing factor) and have been implicated in the rewarding effects of food, cannabinoids, opioids and serotonin.[48] Moreover, neurons in ventral tegmental area and/or nucleus accumbens express GLP1, ghrelin, leptin, insulin, orexin and melanocortin receptors, suggesting that these hormones or peptides can influence the rewarding responses to food.[48] Rats that are fed a diet high in saturated fats and refined sugars for two months demonstrate reduced hippocampal brain-derived neurotrophic factor, with a concomitant reduction in synaptic plasticity.[144]

Food addiction pathological mechanisms

The first 1,000 days of life represent a crucial developmental period for the gut-associated immune system and the BGM axis.[23,145,146] Preclinical models of myelination and brain development suggest that the early life microbiome regulates myelination of the prefrontal cortex[147] and facilitates proper striatal synapse function.[148] Additionally, commensal

microorganisms might also have a role in programming the HPA axis for stress responses,[149] a system implicated in obesity and food addiction behavior,[150-153] whereby excess cortisol and related steroids, such as those from a disrupted of HPA axis, can drive adipogenesis[154] and increase food cravings.[152] Early life exposure to different microorganisms, antibiotics, dietary factors and stress shape the relative abundances and richness of the gut microbiota, influence immune system and brain development, modulate microbial communication with the CNS and program maladaptive BGM interactions.[8,155,156] Although these interactions and their roles in the development of obesity have been well described (Figure 3),[8,155,156] their links with maladaptive eating behaviors is incompletely understood.

Prenatal developmental influences

Maternal prenatal factors have been shown to influence development of the infant BGM axis, with evidence suggesting an important role of the prenatal maternal diet in influencing the neonate gut microbiome. For example, greater maternal consumption of dairy during pregnancy was positively associated with a greater relative abundance of members of the genus *Clostridium* in the faecal microbiome of 145 infants, adjusted for maternal BMI, feeding method and parity.[157] Similarly, a maternal high-fat diet was associated with depletion of the genus *Bacteroides* in the neonatal gut microbiome, which persisted through 4–6 weeks of age.[158] These changes might be mediated indirectly by maternal dietary influences on the composition of breast milk, or directly from effects of the maternal diet on the fetal gut microbiome.[157,158,159] Maternal psychosocial stress has been implicated in the development of an obese phenotype. For example, severe maternal stress due to bereavement in the prenatal period was associated with increased BMI in the male adult offspring in a study of 120,000 men, regardless of trimester that the bereavement occurred in.[160] In mice, moderate maternal stress during pregnancy was found to influence postnatal brain development and gene expression in the paraventricular nucleus of the hypothalamus, the hypothalamic regulator of the HPA axis, ultimately resulting in deficits of neuroplasticity and central stress responsiveness. This effect was partially mediated by stress-induced alterations in the maternal vaginal microbiome.[161] As maternal antibiotic use during the second or third trimester is associated with an increased offspring risk of obesity regardless of pre-gravid BMI in a study of 436 mother–child dyads,[162] and the vaginal microbiota play an important part in shaping the infant microbiome, as demonstrated in a very well-characterized group of 9 mothers and their 10 newborns,[163] it is possible that changes in maternal vaginal microbial abundance associated with antibiotic exposure or diet during pregnancy might also increase the risk of obesity in the offspring.

Postnatal influences

Early diet.—The infant gut microbiota is sensitive to early life nutrition. Human breast milk contains >200 different human milk oligosaccharides (HMOs), a type of prebiotic that cannot be degraded by gut glycoside hydrolases or absorbed via intestinal membrane transporters, suggesting that their primary target is the infant's gut microbiota.[164] The limited small intestinal bioavailability of HMOs enables efficient delivery to the developing infant gut microbiota, most notably *Bifidobacterium*, which can degrade these sugars.[164] Exclusively breastfed infants show a more diverse *Bifidobacterium* microbiota (175 faecal samples from 7 infants) compared with exclusively formula-fed infants (154 faecal samples

from 7 infants), which might set the stage for future, beneficial BGM interactions[165] given that a robust *Bifidobacterium* community has been shown to be protective against intestinal infections[166] and associated with appropriate development of the infant immune system.[167] Limited data exist on the effect of combination feeding (breastmilk and formula) on the gut microbiome, despite how common it is.[168] Bogen et al.,[169] in an observational study of over 70,000 infants, suggest that a longer duration of partial breastfeeding is necessary to yield a similar protective effect against obesity compared with exclusive breastfeeding; combination feeding for >26 weeks yielded a similar protective effect (odds ratio (OR) of developing obesity: 0.70; 95% CI: 0.61–0.81) as exclusive breastfeeding for 16–26 weeks (OR: 0.71; 95% CI: 0.56–0.92).

The relative abundances of the infant gut microbiota and its associated microbial transcriptome change substantially once solid food is incorporated at around 9 months of age, including increased abundances of Bacteroidetes and elevated SCFA levels, as suggested by a high-quality, 2.5-year case study of 60 faecal samples from a single infant[170]. However, evidence has shown that the faecal microbiota profile assessed at 3 months of age (composed of primarily Bacteroidaceae, Bifidobacteriaceae, Enterobacteriaceae, Lachnospiraceae, Ruminococcaceae, and Veillonellaceae) is a more reliable predictor of future risk of being overweight compared to querying the microbiota profile at 12 months, as suggested by a study of 1,087 infants[171] These findings are supported by a meta-analysis of >200,000 participants that found that breastfeeding was associated with a statistically significant reduced risk of obesity in children (pooled adjusted OR: 0.78; 95% CI: 0.74–0.81), with a subset of studies even revealing a dose–response relationship between breastfeeding duration and a reduction in obesity risk.[172]

Highly processed foods, which are filled with large amounts of salt, sugar, fat and additives have become increasingly available in the developed world.[173,174] A pattern of increased exposure and ingestion of such foods in childhood might program food preferences and increase the risk of the development of food addiction into adulthood.[175] Additionally, the relentless marketing of such foods, starting in childhood, has contributed to the increased uncontrollable consumption and cravings of unhealthy foods, especially in children.[176,177]

Antibiotics.—An analysis of outpatient antibiotic prescription rates in 2010 found that >70% of prescriptions in the USA were written for antibiotics, with the highest prescribing rates for children under 10 years of age and with an average of three doses of antibiotics by the age of 2 years.[178] In a USAcohort study of 333,353 children, antibiotic prescriptions were significantly associated with a diagnosis of childhood obesity (HR: 1.26; 95%CI: 1.23–1.28).[179] In a longitudinal study of 39 healthy children, the gut microbiota of antibiotic-treated children was found to be less diverse at multiple phylogenetic levels, with some species even dominated by a single strain. However, the gut microbiome, largely appeared to return to baseline within 1 month of antibiotic exposure.[180] In a Danish study examining over 28,000 mother–child dyads, early administration of antibiotics – within the first 6 months of life – was associated with an increased risk of being overweight at a 7-year follow-up in children from normal weight, but not overweight, mothers; the gut microbiota of study participants were not examined in this study.[181] Though it is difficult to draw definitive conclusions from natural history and cross sectional epidemiological studies,

numerous preclinical studies[182-185] also support a negative effect of early life antibiotics on energy metabolism, the immune system and obesity. Mice that received a single dose of low-dose penicillin at birth showed enhanced high-fat diet-induced obesity as adults; this phenotype could be successfully transferred to germ-free mice by the penicillin-selected microbiota.[182] Another mouse study showed that a single early-life macrolide antibiotic course resulted in persistent perturbations to the gut microbiome (increased *Akkermansia muciniphila* attributed to reductions in competitor mucin-degrading bacteria) and the immune system (reduction in small intestinal $CD4^+$ $IL\text{-}17A^+$ lymphocytes, decreased intestinal IgA secretion).[186] Collectively, these studies suggest that the antibiotic-altered microbiota, and not the antibiotic itself, has a causal role in driving obesogenic metabolic and immunological changes in mice. It remains to be determined if and how the antibiotic induced microbiome alterations can influence the brain and alter ingestive behaviors.

Early adversity.—A history of early adverse life events (EALs) such as natural disaster, parents divorcing, emotional or physical abuse, sickness or death of a family member, predisposes individuals to develop obesity and food addiction in adulthood, mainly through mechanisms associated with stress, inflammation, emotional perturbations, maladaptive coping responses and metabolic disturbances.[187,188] Studies including a meta-analysis have demonstrated that trauma and abuse during the developmental period is significantly associated with greater odds of adulthood obesity and substance abuse (OR: 1.34, 95% CI: 1.24–1.45, $P<.001$).[189-191] Preclinical models of early adversity (maternal separation model) have observed that addictive behaviors can develop later in life, but these animal models require further investigation in humans, especially as the underlying mechansims are unknown and these animal studies are poor models of human behaviour.[192] For example, rats exposed to limited nesting stress in the post-natal period had an immature HPA axis, which was associated with reduced gut microbiota diversity, with an especially notable reduction in bacteria capable of degrading fiber.[193] Although the causal relationship between adversity during childhood and adult obesity is incompletely understood, it has been suggested that overconsumption of highly palatable foods even when hunger and satiation have been met are a possible coping mechanisms to deal with the increased stress responsiveness seen in individuals with a history of EALs.[194-197] In a study of 186 men and women comparing healthy individuals with those with obesity, a history of EALs was associated with alterations in resting state functional connectivity, shown using MRI of brain regions in the extended reward network.[198] These EAL-related alterations probably contributed to an increased probability of developing food addiction and obesity later in life. In a network analysis, sex-differences were also noted in the interactions between early life adversity, brain connectivity and food addiction, suggesting that the development of food addiction might be driven by different factors in men versus women.[198] For example, compared to men, women show increased post-prandial activations in the brain's reward regions, which might increase susceptibility to cravings for highly palatable foods and result in hyperphagia.[199,200] Although the exact molecular mechanisms by which women, compared to men, experience this increased susceptibility remain unclear, results from a pilot study of 63 individuals with varying BMI levels suggest that EALs might contribute to the development of food addiction by interfering with interactions between the brain and gut

microbiome, specifically microbial tryptophan metabolism and reward brain regions such as the amygdala, anterior insula and nucleus accumbens.[201]

Adult environmental influences.

Several environmental factors might contribute to the pathophysiology of obesity by influencing BGM interactions in the adult. Below we discuss some of these environmental factors in detail.

Diet.—Cheap, highly processed and easily accessible high caloric and palatable foods are abundant in the developed world.[202] Studies have shown that foods that are enhanced for taste and salience not only increase cravings and ingestion of these foods, but contextual factors such as stress can serve as conditional cues for future food intake and long-term weight gain.[125,203,204] In fact, overconsumption of highly palatable foods, in particular those containing high levels of fat and sugar, reduces the rewarding thresholds of such foods when ingested, in relationship to reduced levels of dopamine and dopamine receptors in the brain, therefore requiring an increased intake of such foods to generate the same satisfaction.[205,206] Although long-term ingestion of such highly palatable foods has been shown to alter gut microbial diversity and relative abundances in humans, it is important to note that the adult microbiome is relatively resistant to short-term changes in diet, as suggested by a high-quality study of 98 individuals.[207,208]

Food cues.—Studies have shown that portion sizes are directly related to a compromised ability to control food intake, an important feature of food addiction.[209] Food labels and plate and utensil sizes can moderate the portion control effect by increasing food intake.[210] Although the exact mechanisms are unknown, these development and marketing driven food-related cues, which are ubiquitous in Western media and marketing, influence individuals with obesity to consume a greater number of calories than lean individuals.[211,212,213,214] Individuals with obesity have also reported an increased preference and craving for foods rich in fat and sugar, in a study of over 46,000 adults.[215]

Psychosocial stress.—Psychosocial stress can also stimulate ingestive behavior in the adult by increasing appetite, cravings and motivation to consume highly palatable foods, thereby contributing to stress-related weight gain in obesity.[125,216,217] In individuals with obesity, strong associations have been shown between perceived stress and food addiction, snacking, cravings and abnormal eating patterns.[124,218] For example, a study of 339 adults (mean BMI = 26.7 ± 5.4 kg/m^2) demonstrated that chronic stress can influence levels of the orexogenic hormone insulin, as well as glucose and cortisol responses, which in turn can lead to increased food intake and weight gain.[219] Paradoxically, although the ingestion of ‘comfort foods’ high in fat and sugar can reduce subjectively perceived stress, various studies have shown that ingestion of such foods can also lead to increased autonomic responses, disrupt the HPA axis and increase cortisol and ghrelin levels, which have been associated with increased cravings and ingestive behaviors.[132,220-222]

In a mouse model, chronic psychosocial stress resulted in a global reduction in gut microbiota richness and diversity, including a reduction of the relative abundance of

Akkermansia[223], which has been suggested to have beneficial effects within the context of human obesity and metabolic syndrome by previous investigations.[224] These stress-induced perturbations were also associated with changes in the functional profile of the gut microbiome, with decreased synthesis and metabolism of SCFAs, tryptophan and tyrosine.[223] These changes might have been mediated, at least in part, by alterations in immunoregulatory signals, as these mice showed transient elevations in number of IL-10$^+$ T regulatory (T_{reg}) cells, which were suppressed over time.[223]

Amino acid metabolites.—Tryptophan and its metabolites – serotonin (5-HT), kynurenine and indole – have been implicated as important mediators of BGM interactions within the context of obesity and food addiction.[225,226] 5-HT, due in part to its diverse roles as a neurotransmitter in both the gastrointestinal tract (that is, in processes such as peristalsis, secretion and absorption) and the CNS (that is, in regulation of pain modulation, sleep and mood), is the most extensively studied of these metabolites.[227] 95% of the body's 5-HT is stored in gastrointestinal enterochromaffin cells (ECCs) and the gut microbiota, through the production of SCFAs and secondary bile acids, can regulate 5-HT synthesis and its release from ECCs.[228-230] Human studies incorporating acute tryptophan depletion (typically involving providing individuals with a large protein load containing non-tryptophan large neutral amino acids to saturate amino acid blood-brain barrier transporters, thereby limiting the transport of endogenous tryptophan), a validated method to transiently reduce peripheral and central 5-HT synthesis, underscore the effect of changes in 5-HT release on food preference.[231] In a study of 55 women following acute tryptophan depletion, participants with overweight showed a statistically significant increase in sweet calorie intake and preference for sweet foods compared with a placebo intervention.[232] By contrast, the lean group showed no differences, suggesting that individuals with overweight might be more susceptible to changes in tryptophan metabolism and 5-HT availability.[232] Host and microorganisms participate in different aspects of tryptophan metabolism: although host cells have the major role in the kynurenine pathway, microbial cells are primarily involved in the indole pathway.[233]

Although 5-HT has been the most extensively studied tryptophan metabolite, the majority of tryptophan is converted by host cells to kynurenine.[234] In the gastrointestinal tract, kynurenine is synthesized from tryptophan by the rate limiting enzyme indoleamine-2,3-dioxygenase (IDO), which can be upregulated by inflammatory cytokines or downregulated by reactive oxygen species, such as hydrogen peroxide produced by intestinal *Lactobacillus*.[235,236] As both kynurenine and tryptophan compete to cross the blood–brain barrier through the same, easily saturated transporter, inflammation-associated or microbiota-associated changes in peripheral kynurenine concentrations might also influence central 5-HT levels.[237] Alternatively, increased flux through the kynurenine pathway can influence the brain through neuroactive downstream metabolites such as kynurenate and quinolinate, which function as an N-methyl-D-aspartate (NMDA) antagonist and an NMDA excitotoxin or neurotoxin, respectivly.[235] The balance of tryptophan metabolism might be preferentially shunted towards the kynurenine pathway in individuals with obesity, as serum kynurenine, kynurenate and quinolinate levels show positive associations with BMI.[238]

Another important group of tryptophan metabolites are the indoles. Most undigested dietary tryptophan in the gut lumen is converted exclusively by gut microorganisms to indole.[239] In animal and human studies, indole has been shown to play an important part in modulating kynurenine synthesis[7], strengthening the mucosal intestinal barrier,[14] attenuating CNS inflammation,[15] and modulating GLP1 secretion,[240] all of which have been shown to be disrupted in states of obesity.[238,241-243] One study investigating the role of stool indole metabolites in 63 healthy individuals found positive associations between indole, skatole and indoleacetic acid and food addiction behaviors, with regions of the extended reward network (nucleus accumbens, amygdala, and anterior insula) playing an important part in this interaction.[201]

Metabolic toxaemia.—In mouse models of obesity, a diet high in fat (60% lard) and low in dietary fibre has been implicated in the longterm disruptions in gut microbiota diversity, [244] while diets high in fibre result in positive alterations in ingestive behavior (decreased food intake, increased satiety)[245]. When dietary fiber is reduced or unavailable, certain gut microorganisms such as *Akkermansia mucinophilia* consume the glycans making up mucins in the mucus layer of the gut, thereby compromising intestinal barrier function.[246] This phenomenon is referred to as increased 'leakiness' of the gut (Figure 4). Sonnenburg et al. [244] showed in mice that a low fibre diet results in a substantial loss of microbiota diversity and abundance, which was magnified in each successive generation, up to the fourth and final generation studied.[244] Remarkably, supplementation with a high fibre diet alone was insufficient to normalize microbial diversity.[244] Reduced intestinal barrier function results in increased access of membrane bound lipopolysaccharide (LPS) from Gram-positive microorganisms to TLR4 receptors on host epithelial and immune cells, contributing to inappropriate immune activation.[247-250]

The combination of a leaky gut and an overabundance of inflammatory bacterial products is thought to result in elevated plasma levels of LPS and proinflammatory cytokines, including IL-1β, IL-6 and TNF.[251] Increased systemic immune activation can shift tryptophan metabolism towards the kynurenine pathway and away from 5-HT or indole synthesis, as described previously.[252] This state of metabolic endotoxaemia has been shown to reduce central satiety mechanisms by influencing enteroendocrine secretion of the satiety hormones PYY, cholecystokinin and 5-HT[253-255] and by reducing the expression of anorexigenic peptide receptors and leptin receptors on vagal afferents[256] and in the hypothalamus, respectively.[257] In this way, vagal afferent neurons in the presence of a high-fat diet remain in an orexigenic state, regardless of whether food was consumed, driving hyperphagia and obesity.[258] In addition to changes in ingestive behavior, there are likely numerous other mechanisms contributing to high-fat diet-induced obesity, such as gut microbiota-driven remodeling of the intestinal transcriptome to favor an obesogenic signaling cascade.[259]

Although the gut microbiota has an important role in the generation of inflammatory mediators, it might also be protective against the development of metabolic endotoxaemia. For example, mice fed a high-fat diet that was supplemented with oligofructose, a prebiotic fiber that preferentially increases gut *Bifidobacterium* abundance, showed reduced endotoxaemia, decreased levels of plasma and adipose tissue proinflammatory cytokines, and improved glucose tolerance.[260] In this study, no relationship was seen between

endotoxaemia and any other bacterial group except for *Bifidobacterium*.[260] The translatability of these preclinical findings to human metabolic disease remains to be determined.

In summary, disruptions during both early life (prenatal influences, including maternal diet, antibiotic exposure and early adversity) and adulthood (diet and/or psychosocial stressors) can have a profound effect on the gut microbiome and the brain, setting the stage for food addiction. The associated changes in amino acid metabolism and metabolic toxaemia perpetuate these maladaptive changes at all levels of the BGM axis (Figure 1).

Clinical implications of food addiction

The proposed system biological model of altered BGM interactions resulting in maladaptive changes in ingestive behavior provides not only a plausible explanation for the refractory nature of obesity to many traditional therapeutic strategies, but also presents a rationale for several new therapeutic strategies (Figure 5, Box 1).

Gut-directed therapies

As the gut is the primary source of hunger and satiety signals that regulate homeostatic feeding behaviors, it is not surprising that several obesity treatments, including bariatric surgery, have aimed to modify these gut mechanisms. Most of the bariatric procedures result in satisfactory and sustained weight loss and prompt resolution of the metabolic syndrome, a substantial improvement over the transient and more modest effects seen with medical therapies.[261,262] Bariatric surgery-related weight loss is multifactorial, with the most common procedures, Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG), resulting in hypophagia. This hypophagia is not only a consequence of a reduced gastric capacity but also of marked reductions in appetite, food preferences and food addiction,[263-265] which predicted long-term weight loss outcomes.[266-268] Evidence also exists for the role of bariatric surgery-induced weight loss driving remission of food addiction (as assessed by YFAS); one study of 14 patients with obesity and with food addiction prior to surgery demonstrated remission of food addiction in 93% following surgery-induced weight loss ($P<0.001$).[269] The mechanisms behind the post-bariatric surgery reductions in food addiction scores and brain responses to highly palatable food cues, as suggested by the aforementioned small, pilot studies, are incompletely understood.[263,265] Both, RYGB and LSG result in increases in blood levels of anorexigenic gut peptides (GLP1, PYY) that, in part, mediate changes in appetite and food addiction after bariatric surgery.[263,270-272] However, several other BGM pathways have also been implicated from both preclinical (mouse models) and clinical studies as possible explanations for these changes, including enhanced microbial production of polyamines and GABA, changes in bile acid profiles and FXR pathway signaling, and increased production of SCFAs.[273-277] Preliminary work in individuals with obesity undergoing bariatric surgery suggest that changes in gut microbiome composition and microbial metabolism of aromatic amino acids and glutamate were associated with reductions in appetite, food addiction and changes in food preferences, suggesting a possible causal role of these metabolites in behavioral responses.[278-283] However, future studies are needed to confirm causality between gut

microbial metabolites and food addiction in humans. Another important consideration is the well-known reduction in systemic low-grade inflammation and endotoxaemia seen after bariatric surgery.[284] As discussed earlier, this anti-inflammatory effect could increase hypothalamic sensitivity to satiety signals and to insulin, resulting in a shift towards more homeostatic regulation of ingestive behaviors.[285-290] Some studies have suggested that because of the involvement of the brain's reward system in both food addiction and addiction of other substances, bariatric surgery might increase alcohol use.[291]

Microbiome-directed therapies

Microbiome-directed therapies, including faecal microbiota transplantation (FMT), represent a novel therapeutic option for obesity and metabolic syndrome. Small clinical studies (one study had 18 individuals, 9 receiving autologous FMT and 9 receiving allogenic FMT from a lean donor, and a second study had 38 individuals, 12 receiving autologous FMT, 26 receiving allogenic FMT from a lean donor) have shown that FMT from a lean donor resulted in an increase of butyrate-producing bacteria and improved insulin sensitivity in recipients with metabolic syndrome.[292,293] The improved insulin sensitivity and associated changes in the faecal microbiome were not sustained at 18-week follow-up, suggesting a resilient faecal core microbiome.[293] It remains unclear if FMT, when combined with lifestyle modification and brain-directed therapies, might result in longer-term success. Notably, lower recipient baseline faecal microbiota diversity was predictive of success of FMT.[293] Ingestive behaviors were not assessed in those studies. It is well known that microbial products such as SCFAs modulate feeding behavior via central mechanisms.[19] For example, the intake of a type of fiber that selectively increases gut microbial propionate production was associated with lowering the subjective appeal and the brain reward activation (as measured by brain MRI) to highly-palatable-food pictures in a study of 20 healthy men without obesity.[21] It is important to note, however, that FMT is not without risks, including the rare but well-documented risks of bacteraemia or sepsis, ileus, perforation and aspiration, in addition to the more common, transient gastrointestinal complaints such as abdominal pain or changes in bowel habit.[294]

Time restricted eating

Increased interest exists in the potential health benefits of different types of time-restricted feeding (TRF) on obesity, cardiovascular health and ageing, including intermittent feeding and the fasting mimicking diet.[295-297] In mice, ad libitum exposure to a high-fat diet resulted in changes in circadian rhythms and feeding behaviors that led to increased energy intake and weight gain.[298] These changes could be reversed by TRF.[299] One study showed that individuals with overweight, but otherwise healthy, adhering to TRF with the assistance of a smartphone application significantly reduced their daily-energy intake, in part by reducing late-night intake of alcohol and snacks. This behavioral change resulted in sustained weight loss up to 1 year after the intervention.[300] The role that the microbiome plays in mediating the effects of TRF in humans is not known. However, in animal and in humans, gut microbiota composition and function display oscillations during the day that are associated with the circadian rhythm of the host and are dictated by the host's food intake patterns.[301] These oscillations in microbial metabolite production might have a major effect on the circadian epigenetic and transcriptional landscape of the gut and the liver, and eating

behaviors leading to compromised oscillations have been associated with obesity and metabolic syndrome.[302] There are other potential factors that might contribute to the benefits of TRF, including reduction of intake of snacks and calories, and changes in the gut microbial environment due to an increase in fasting associated patterns of motility and secretion.

Brain-directed therapies

Based on the premise that obesity is the result of an imbalance between energy intake and expenditure, for many years the dominant pharmacological approach to obesity was based on molecules that decrease appetite and/or stimulate energy expenditure.[303-305] Of the medications now available for weight loss in the USA, some are aimed to decrease appetite by directly affecting the hypothalamus (phentermine, bupropion, naltrexone, or locarserin). Others are aimed to modulate reward circuits in the brain (naltrexone, bupropion, or topiramate), reducing the subjective pleasantness of palatable foods and compulsive food cravings, as well as decreasing the response to food cues at reward regions in the brain.[306-309] A dual effect, reducing appetite and reward-based eating, is achieved through the use of hormonal satiety signals, like GLP1 agonists (liraglutide or exenatide).[278,310] Very little is known about the effect of these anti-obesity medications on the gut microbiota. A small study in 19 individuals with type 2 diabetes mellitus have shown that treatment with liraglutide for 42 days resulted in a statistically significant increase in relative abundance of the genus *Akkermansia*.[311]

Cognitive behavioral therapy (CBT) in individuals with obesity with food addiction aims to change specific thoughts, beliefs, and cognition directly related to the feelings and behaviors attributed to uncontrollable ingestive behaviors and cravings.[312,313] Since CBT strengthens prefrontal control mechanisms,[314-319] cognitive reappraisal and attention strategies through CBT are thought to strengthen the inhibitory control of the prefrontal regions on the extended reward networks by influencing appetitive motivation and reducing food addiction in individuals with obesity.[320-323]

Key open research questions and future directions

Considerable progress has been made in our understanding of changes in BGM interactions in food addiction and obesity; yet, the majority of studies have been performed in rodents and there are few longitudinal, mechanistic studies in humans that support the translational relevance of these findings, which would guide more effective therapies. There is currently no evidence in humans that food addiction is the result of an altered gut microbiome, or that food addiction is driven by particular gut microbial metabolites. Furthermore, given the complexity and bidirectional signaling within the BGM axis, it is unlikely that a single microbial metabolite could causally explain the behavioral changes. Considering the influence of early life experiences, environmental factors, stress, emotions, genetic factors, and dietary influences in humans, microbial influences might only explain a small component of the variance in the development of food addiction. Several approaches are necessary to move this field beyond the current reliance on largely associative studies in small populations. Microbiome characterization by shotgun metagenomics,

metatranscriptomics and proteomics studies in well phenotyped human populations combined with big data analysis will be required to identify a microbial signature of food addiction. At the same time, mechanistic studies using targeted interventions, which have been shown to be effective in reducing predominantly hedonic driven eating behaviors in humans, such as bariatric surgery, TRF or cognitive behavioral therapy are needed to probe for a causal role of the gut microbiome. Such human studies should be combined with reverse translational studies, evaluating the effect of faecal microbial transfer on rodent feeding behaviors and body weight.

Conclusions

Altered BGM interactions manifesting as dysregulated eating behavior and resulting in obesity, can best be understood as a complex, circular system that is stable and highly resistant to change (Figure 4). The close interactions between diet and gut microbial signals, the effect of these signals on satiety and inflammatory mediators from the gut, and their disruptive effect on homeostatic mechanisms in the brain, leads to a shift towards a greater influence of hedonic reward mechanisms and a reduction in inhibitory control. These changes in turn drive the preferred intake of high caloric foods reinforcing the gut dysbiosis (Figure 4). As traditional therapies aimed at individual aspects of this system, including most traditional dieting strategies, have failed, novel therapies must be based on a new understanding of the systems properties of BGM interactions (Figure 1). A combination of therapeutic approaches targeting different nodes of this system, and individualization of treatments based on differences in gut microbial composition and function are required to provide greater clinical benefits.

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Glossary

Systems biology:
An interdisciplinary field of study that focuses on complex interactions within multiple biological systems, rather than focusing on individual mechanisms.

Hedonic-driven eating behaviors:
Also known as ‘food addiction’, these behaviours correspond to the continued consumption of highly palatable foods even after energy requirements have been met.

Dopaminergic reward system:
Refers to the extensive network of neurons in the extended reward network that depend on dopamine as the primary neurotransmitter for reward-related processing.

Extended reward network:
Used interchangeablely with ‘greater reward system’, this term describes brain regions concerned with interconnecting brain networks such as reward and salience networks, and is associated with processing of rewarding stimuli and modulation of food-seeking behaviors.

Neural substrates:
A brain region or network that is associated with a specific behavior.

Cortical performance monitoring:
Refers to processes associated with reward sensitivity, motivation, interoceptive awareness, stress reactivity and self-control.

Salience:
The salience brain network is responsible for monitoring the homeostatic state of the body to make adaptive adjustments to real or expected disturbances in homeostasis through the autonomic nervous system and behavioral responses.

Corticostriatal communication:
Refers to the extensive communication network between the brain’s cortex, which houses the extended reward network (including the frontal cortex and insula), and the striatum, which houses the core reword network (nucleus accumbens, basal ganglia).

Ventral tegmental area:
Key region of the midbrain that houses the dopaminergic cell bodies that project to all regions of the core and extended reward network.

Nucleus accumbens:
Region of the basal ganglia and a key hub for the core reward system, responsible for many dopaminergic processes, especially those related to pleasure, motivation, and aversion.

Prebiotic:
Refers to dietary fibre or other substrates that can only be digested by commensal gut microorganisms, thereby promoting gut microbiota diversity and health.

Maladaptive coping:
Behaviors that are used to cope with situations to alleviate stress or symptoms, but are not necessarily healthy and do not address the core cause of the stress.

Psychological stress:
Sufficient levels of stress orginating from the environment that can cause dyregulation of homeostatic responses to cause physical or psychological symptoms.

Perceived stress:
A measure of the degree to which events in an individual’s life are assessed as stressful. The most widely used scale for perceived stress is the Perceived Stress Scale.

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Box 1 |

Therapeutic targets within the brain gut microbiome axis for obesity

Brain Targets	Approaches for Obesity Treatment
Cognitive Control	• Cognitive behavioral therapy
Reward Processes	• Topiramate + Phentermine • Bupropion + Naltrexone • GLP-1 agonists (e.g. Liraglutide)
Homeostatic Control	• Serotonin modulators (e.g. Lorcaserin) • Amphetamine class (e.g. Phentermine) • GLP-1 agonists (e.g. Liraglutide) • Leptin agonists • Vagus nerve electrical modulation
Gut Remodeling	• Bariatric surgery (e.g. RYGB, LSG) • Bariatric endoscopy (e.g. gastric balloons, gastric plication, gastric content aspiration)
Gut Absorption	• Lipase inhibitors (e.g. Orlistat) • Mucosal barriers/ablation (e.g. duodenal sleeve)
Gut Microbiota	• Prebiotics (e.g. oligofructose, oligosacharides) • Probiotics (e.g. Lactobacillus) • Bariatric surgery • Fecal transplant

Key Points

- Food addiction refers to maladaptive ingestive behaviors resulting from a shift from primarily homeostatic to hedonic regulatory mechanisms of food intake; this shift reflects alterations at all levels of the brain–gut–microbiome (BGM) axis.
- Normal ingestive behavior is the result of the tightly regulated interplay between orexogenic and anorexogenic gut hormones, leptin signaling from adipose tissue, hypothalamic nuclei, the dopaminergic reward system and prefrontal inhibitory influences.
- In food addiction, a disinhibition of reward and anorexogenic mechanisms at all levels of the BGM axis results in unrestrained craving for food.
- Several adverse early life events, including nutrition, stress and antibiotic intake can influence the development of BGM interactions and of ingestive behavior.
- Lifelong dietary choices can modulate BGM Interactions and eating behaviors; for example, chronic ingestion of a typical Western diet can result in systemic low-grade immune system activation that can reduce feedback inhibitory mechanisms restraining food intake.
- Current pharmacological treatment options for food addition are limited, bariatric surgery is the only therapy providing long-term benefits, but novel treatment approaches (including time restricted eating and cognitive behavioral interventions) are being evaluated.

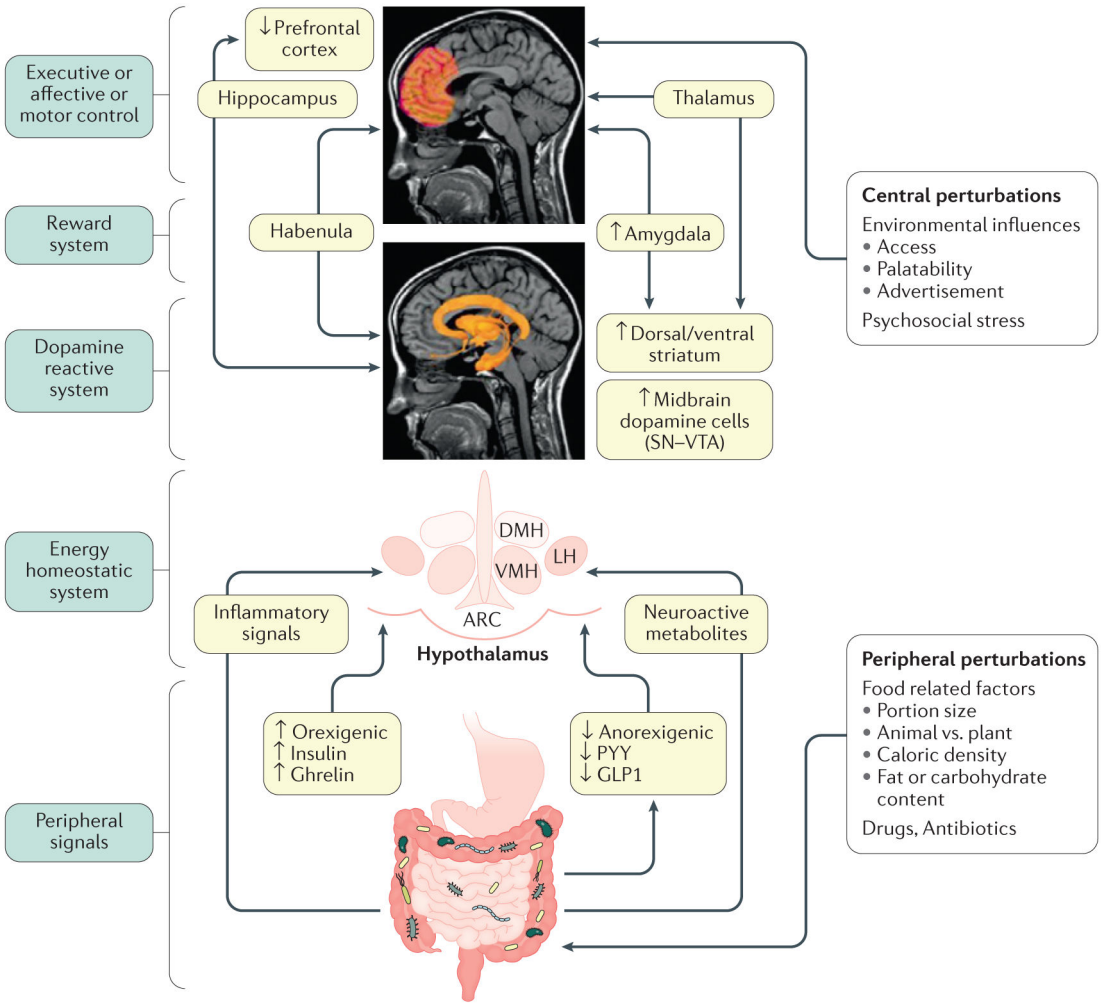

Figure 1. Model of brain–gut–microbiome interactions in ingestive behavior.

In the periphery, gut-generated and vagally transmitted orexogenic and anorexogenic signals interact with specific nuclei in the hypothalamus in the homeostatic regulation of food intake. Food-related factors interact with gut microorganisms and gut microbial metabolites modulate the release of orexogenic and anorexogenic peptides from enteroendocrine cells in the distal small intestine, shifting the balance between anorexogenic and orexogenic signaling in the hypothalamus. In addition, gut microorganisms can signal to the brain via inflammatory mediators (such as lipopolysaccharides) and neuroactive metabolites (such as tryptophan metabolites). Centrally, interactions between several brain networks, including the prefrontal cortex, the dopaminergic reward system and the sensorimotor system underlie the hedonic regulation of food intake. Several environmental influences such as food advertisements, food cues engage the extended reward system which can override the homeostatic control mechanisms. Exposure to visual and sensory cues, as well as psychosocial stress play important role in this process. Blue boxes on the left represent different parts of the BGM axis. Light green boxes in the center show mechanisms involved in altered BGM interactions in food addiction. Upward arrows show upregulation,

downward arrows show downregulation. Modified with permission from Volkow et al. Biological Psychiatry 2013 EM: DONE

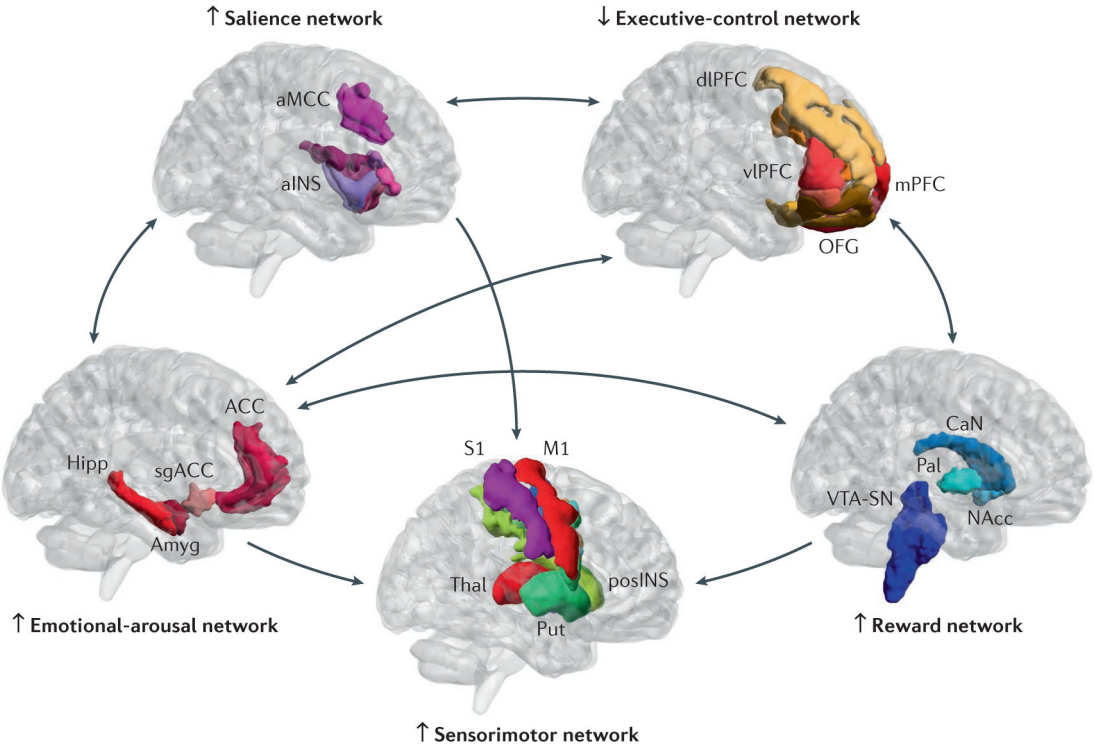

Figure 2. Model of altered brain network interactions in food addiction.

Several brain networks interact in the regulation of ingestive behavior. In food addiction, increased engagement of the salience network by food cues engages the executive control network leading to increased attention to food, and the emotional arousal network. Insufficient inhibitory control of the reward and of the emotional arousal networks by the executive control network plays a key part in shifting the balance from predominantly homeostatic to hedonic and regulation of food intake. The **salience network (**aMCC, anterior mid cingulate cortex; aINS, anterior insula) responds according to the subjective salience of any interoceptive or exteroceptive stimulus reaching the brain, or to the expectation of such stimuli, and coordinates appropriate attentional, behavioral, affective and visceral autonomic responses to such stimuli. The **executive control network (**dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; mPFC, medial prefrontal cortex; OFG, orbitofrontal gyrus) is activated during tasks involving executive functions such as attention, working memory, planning and response selection. Under normal circumstances, it exerts an inhibitory influence on the emotional arousal and the reward networks. The **reward network (**Nacc, nucleus accumbens; VTA-SN, ventral tegmental area – substantia nigra; CaN, caudate nucleus; Pal, pallidum) is a group of neural structures responsible for motivation, ‘wanting’ desire or craving for a reward. It is under inhibitory control by the executive control network. Its main neurotransmitter is dopamine. The s**ensorimotor network (**Thal, thalamus; Put, putamen; pINS, posterior insula; S1/S2, primary/secondary sensory cortex; M1/M2, primary/secondary motor cortex) receives sensory input from the body, is important for awareness of body sensations and the generation of appropriate motor responses and behaviors.

The **Emotional arousal network (**ACC, anterior cingulate cortex; Hipp, hippocampus; Amyg, amygdala; sgACC, subgenual anterior cingulate cortex) is activated by perceived or real perturbation of the organism's homeostasis. Bidirectional arrows between brains depict reported bidirectional network interactions. Up and down arrows next to brains illustrate reported up and down regulation of the individual networks

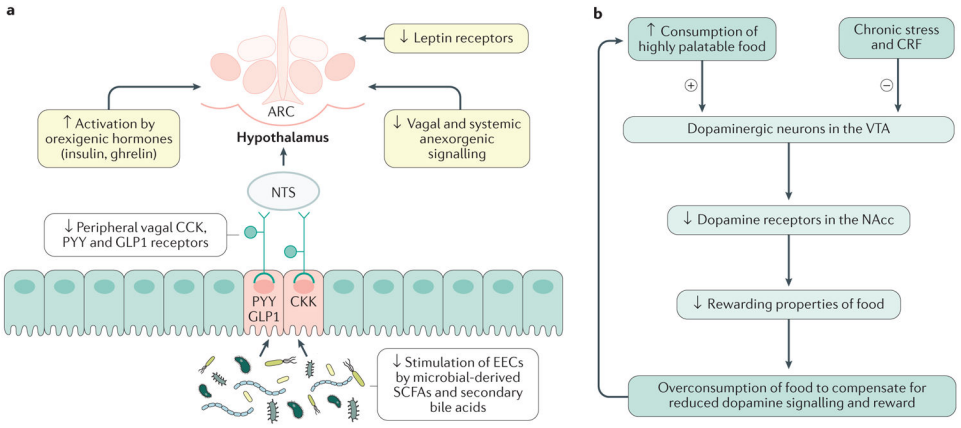

Figure 3. Mechanisms in the homeostatic and hedonic systems leading to food addiction.

a | Diet-induced disinhibition of vagal and hypothalamic satiety mechanisms. A high fat, low fibre diet reduces the release of satiety hormones (GLP1, PYY, CCK) from enteroendocrine cells (EECs) in the gut by dietary fibre-derived short-chain fatty acids (SCFAs), leads to downregulation of receptors for satiety hormones molecules on vagal afferents innervating the EECs, and to a downregulation of the vagally-mediated satiety signaling to the arcuate nucleus of the hypothalamus (ARC). Hypothalamic receptors mediating the effect of other anorexigenic signals (leptin) reaching the ARC via the systemic circulation are also downregulated, resulting in an unrestrained effect of orexogenic signals (ghrelin, insulin, cortisol). Thus, chronic exposure to a high fat, low fibre diet downregulates the inhibitory mechanisms of homeostatic regulation of ingestive behaviors. **b** | Diet-induced changes in the extended reward system. According to the dopamine deficiency hypothesis, a reduction of dopaminergic stimulation of neurons in the NAc as a result of reduced dopamine relase from the VTA, and a downregulation of dopamine receptors on NAc neurons, reduces the rewarding effects of ingested foods, and leads to craving and overconsumption of unhealthy food in an attempt to compensate for the reduced dopamine signaling. Chronic stress-induced CRF release and glucocorticoid levels also have an inhibitory effect on dopamine signaling. Up and downward arrows inside boxes illustrate reported up and downregulation of respective mechanisms.

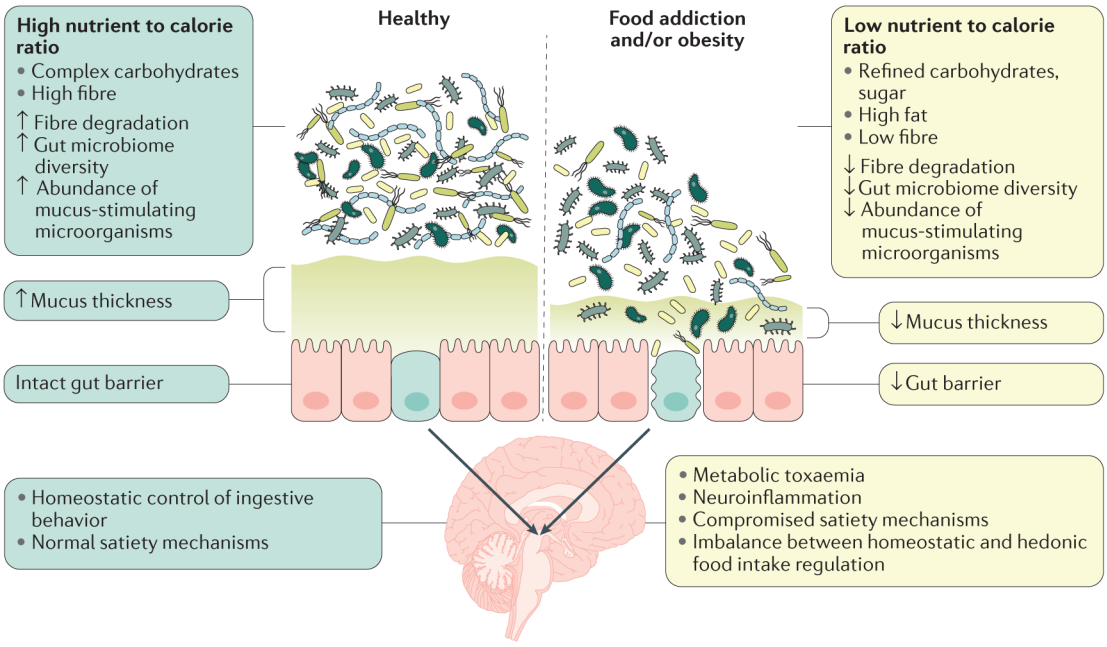

Figure 4. Interactions between food, gut microbiota and intestinal permeability in the regulation of ingestive behavior.

Left panel: A healthy diet (high in fibre, low in fat and sugar) is associated with a high diversity of the gut microbiota, including an abundance of taxa involved in stimulating mucus production in humans and animal models.[323,324] The combination of an intact mucus layer and tight intestinal epithelium results in an intact gut barrier. **Right panel:** An unhealthy diet (high in fat, sugar and low in fiber) is associated with a reduced microbial diversity, reduction of mucus stimulating microorganisms, reduction in mucus layer thickness and an increase in epithelial leakiness. This process results in reduced intestinal barrier function (leaky gut) and activation of the gut associated immune system by microbial products such as lipopolysaccharide (LPS). The combination of a leaky gut and an overabundance of inflammatory bacterial products is thought to result in elevated plasma levels of LPS and proinflammatory cytokines. This state of metabolic endotoxaemia has been shown to reduce central satiety mechanisms by influencing enteroendocrine secretion of the satiety hormones PYY, cholecystokinin and serotonin (5-HT), and by reducing the expression of anorexigenic peptide receptors and leptin receptors on vagal afferents and in the hypothalamus, respectively, leading to a disinhibition of satiety mechanisms. Up and downward arrows inside boxes represent reported up and downregulation of mechanisms and of microbiome measures. Modified with permission from Cani & Everard. Mol. Nutr Food Res 60:58-66; 2016 **OK, but would replace the last one with reduction of net mucus production**

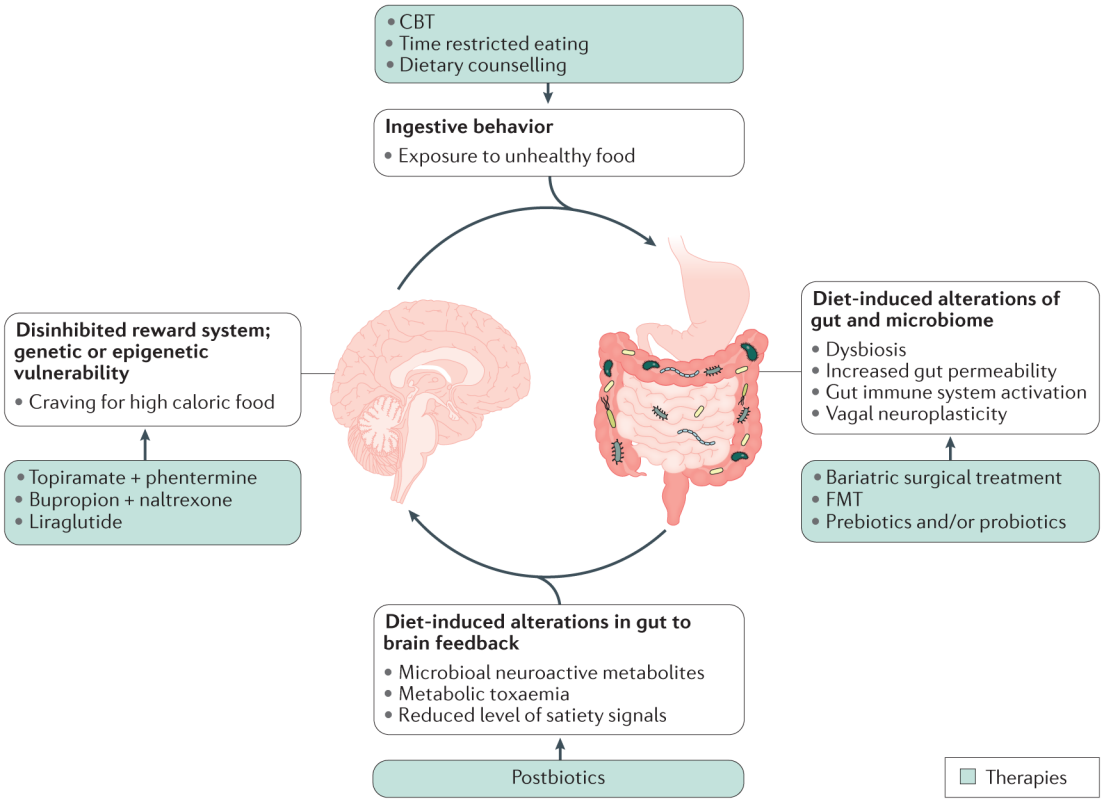

Figure 5. Circular model of brain gut microbiome interactions in obesity and targets for intervention.

The interaction of genetic and epigenetic factors influences the balance between hedonic and homeostatic control of ingestive behavior, and the risk for the development of hedonic dominance. When exposed to ubiquitous food of high caloric density (fat, sugar) and low in fiber, predisposed individual will overconsume such foods, resulting in changes in the gut and the microbiome as shown in Fig. 3. The resulting change in gut to brain signaling can further compromises homeostatic regulation of food intake and reinforces the disinhibition of the reward system. Targets for intervention and therapeutic modalities include altered ingestive behavior (cognitive behavioral therapy, CBT; time restricted eating; dietary counseling), alterations of gut and microbiome (bariatric endoscopic and surgical treatment; faecal microbota transplantation (FMT); prebiotics and probiotics); altered gut to brain feedback (postbiotics such as butyrate, tryptophan derived compounds, including indoles, and other amino acid metabolites.) and altered reward system (centrally acting medications).