Brain–gut–microbiome interactions in obesity and food addiction

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Abstract | Normal eating behaviour is coordinated by the tightly regulated balance between intestinal and extra-intestinal homeostatic and hedonic mechanisms. By contrast, food addiction is a complex, maladaptive eating behaviour 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 signalling 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 signalling) and intestinal (vagal afferent function, metabolic endotoxaemia, systemic immune activation, changes to gut microbiome and metabolome) mechanisms. In this Review, we propose a systems biology 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.

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

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The obesity epidemic continues to be a major public health problem both in the USA and globally[1,2]. Obesity is defined as a BMI of ≥30 kg/m², and a BMI of ≥40 kg/m² is considered extreme obesity, with overweight defined as a BMI of 25–29.9 kg/m² (REFS[1,2]). The prevalence of obesity worldwide has tripled since 1975, with ~39% of the world's adult population having overweight and 13% having obesity in 2016 (REF.[2]). In the USA alone, the number of individuals with obesity continues to dramatically increase, with >35% of individuals having overweight, >37% obesity and 8% morbid obesity[2,3]. Obesity is the biggest driver of preventable chronic diseases and health-care costs in the USA, with current cost estimates in the range US$147–210 billion per year[4]. Despite the magnitude of the problem and the associated health-care 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 signalling within the brain–gut–microbiome (BGM) axis in the pathophysiology of obesity, mediated by metabolic, endocrine, neural and immune system mechanisms[8]. Signalling from the brain through the autonomic nervous system 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] and relative gut microbial abundance[11], as well gene expression patterns in certain 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 (ECCs) and primary or secondary afferent nerve endings. Sensing of bacterial metabolites by these cells results in neural signalling to the brain and 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 by-product of microbial fermentation of dietary fibre, have emerged as key mediators of BGM signalling[19]. SCFAs can influence the central nervous system (CNS) through immune[20], endocrine[21] and vagal[22] pathways.

The gut microbiome and bidirectional BGM interactions are programmed through influences during

Key points

- Food addiction refers to maladaptive ingestive behaviours 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 behaviour is the result of the tightly regulated interplay between orexigenic and anorexigenic gut hormones, leptin signalling from adipose tissue, hypothalamic nuclei, the dopaminergic reward system and prefrontal inhibitory influences.
- In food addiction, a disinhibition of reward and anorexigenic 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 behaviour.
- Lifelong dietary choices can modulate BGM interactions and eating behaviours; for example, chronic ingestion of a Western diet can result in systemic low-grade immune system activation, reducing feedback inhibitory mechanisms restraining food intake.
- Pharmacological treatment options for food addition are limited and bariatric surgery is the only therapy providing long-term benefits; however, novel treatment approaches, including time-restricted eating and cognitive behavioural interventions, are being evaluated.

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 (FIG. 1). Perturbations at any level of the BGM system, resulting in compromised inhibitory mechanisms that normally regulate food intake, can bias ingestive behaviours towards predominantly hedonic-driven eating behaviour, 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 orexigenic and anorexigenic 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 orexigenic (ghrelin, insulin) and anorexigenic 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 behaviour, which has been termed '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 (REF.[39]), there has been an ongoing controversy over the term food addiction[40,41], despite strong arguments supporting shared underlying pathophysiology between drug and food addiction[33,42]. On a behavioural 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 behaviour 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 behaviour 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 using the YFAS is present in only a subgroup of individuals with obesity[46,53]. Questionnaire-based surveys and studies using other methods of assessment have shown that food addiction is present in 25–37% of individuals with obesity, and reaches rates of up to 60% in those who have morbid obesity 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 multiple fields of research including neuroscience, gastroenterology, microbiology, endocrinology, immunology and many others. For example, the gut microbiome, intestinal signalling, extra-intestinal signalling (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, systems-based approach is able to create a more nuanced understanding of food addiction, as shown in FIG. 1. In this Review, we summarize the physiology of food addiction in obesity as it relates to alterations within the BGM. We introduce key factors that influence the BGM axis, such as diet, antibiotics, early-life adversity, food cues and psychosocial stress, during the prenatal

Hedonic-driven eating behaviour
The continued consumption of highly palatable foods even after energy requirements have been met (also known as 'food addiction').

Dopaminergic reward system
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
A network comprising interconnecting brain networks such as reward and salience networks, associated with processing of reward stimuli and modulation of food-seeking behaviours (used interchangeably with 'greater reward system').

Neural substrates
A brain region or network associated with a specific behaviour.

Cortical performance monitoring
Processes associated with reward sensitivity, motivation, interoceptive awareness, stress reactivity and self-control.

and postnatal period, and during adulthood. We also discuss several therapies aimed at food addiction in individuals with obesity, including those targeting the gut, the microbiome and the brain, and highlight limitations and areas for future research in the field.

Ingestive behaviour physiology

The role of the gut microbiome

Ingestive behaviour 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 (FIG. 1).

BGM interactions involving gut peptides that regulate ingestive behaviour 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 signalling mechanisms[65], whereas the intestinal hormones GLP1 (REF.[66]) and peptide YY[67] trigger satiety and associated behavioural changes. Increased production of microbiota-derived

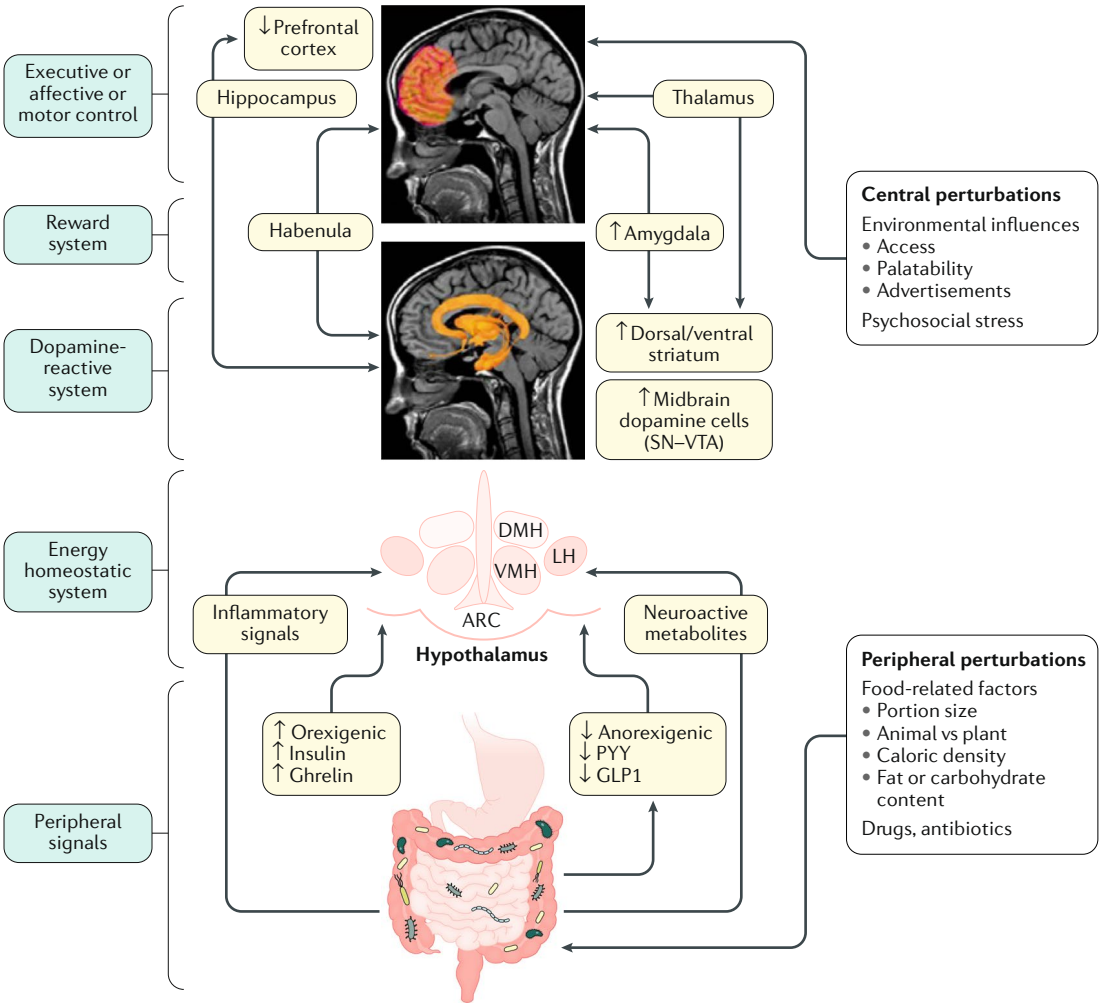

Fig. 1 | **Model of brain–gut–microbiome interactions in ingestive behaviour.** In the periphery, gut-generated and vagally transmitted orexigenic and anorexigenic signals interact with specific nuclei in the hypothalamus in the homeostatic regulation of food intake. Food-related factors interact with gut microorganisms, and gut microbial metabolites modulate the release of orexigenic and anorexigenic peptides from enteroendocrine cells in the distal small intestine, shifting the balance between anorexigenic and orexigenic signalling 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 and 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 part in this process. Blue boxes on the left represent different parts of the brain–gut–microbiome axis and boxes in the centre show mechanisms involved in altered brain–gut–microbiome interactions in food addiction, with upward arrows indicating upregulation and downward arrows indicating downregulation. ARC, arcuate nucleus; DMH, dorsomedial hypothalamic nucleus; GLP1, glucagon-like peptide 1; LH, lateral hypothalamus; PYY, peptide YY; SN–VTA, substantia nigra–ventral tegmental area; VMH, ventromedial nucleus of the hypothalamus. Adapted with permission from REF.[32], Wiley, and REF.[48], Elsevier.

SCFAs can stimulate enteroendocrine cells to release GLP1 (REF.[68]) and peptide YY[69], while decreasing the secretion of ghrelin[70].

Insulin is another orexigenic hormone, as hyperinsulinaemia, regardless of plasma glucose levels, contributes to increased sensations of hunger and results in a heightened palatability of sucrose[71]. Evidence from animals suggests that disruption of microbial SCFA metabolism can promote insulin resistance and hyperinsulinaemia[72], thereby potentially shifting the balance towards hedonic behaviour. 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 signalling 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 induced microbial production of the secondary bile acid lithocholic acid, driving TGR5 signalling 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 in 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 decrease in secondary bile acids as well as in insulin sensitivity[76].

As an example of microbial regulation of food preferences, fruitflies 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 *A. pomorum* nor lactobacilli were capable of modulating food intake individually, suggesting that these microorganisms must work together to influence host behaviour[77]. Although the mechanisms driving food-seeking behaviour in this model remain unclear, microbial modulation of neuronal TOR signalling has been previously proposed as an important mediator of nutrient balance and growth in *Drosophila*[78,79]. In fruitflies 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 CNS TOR kinase, 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 behaviour both in 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 composed 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 behaviour is under the control of the extended reward network, which includes brain regions from the core reward network including the nucleus accumbens, ventral tegmental area and the substantia nigra, and is regulated by cognitive network regions including the prefrontal cortex[88,89]. The extended reward network is involved in the processing of reward stimuli and modulation of food-seeking behaviour[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 the reward network, the salience network, the emotional regulation network, the somatosensory system and the cortical inhibition network (prefrontal control)[31,33,90,99] (FIG. 2). 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 the autonomic nervous system, as well as behavioural 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) signalling, 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

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.

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.

Salience network
The brain network 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 behavioural responses.

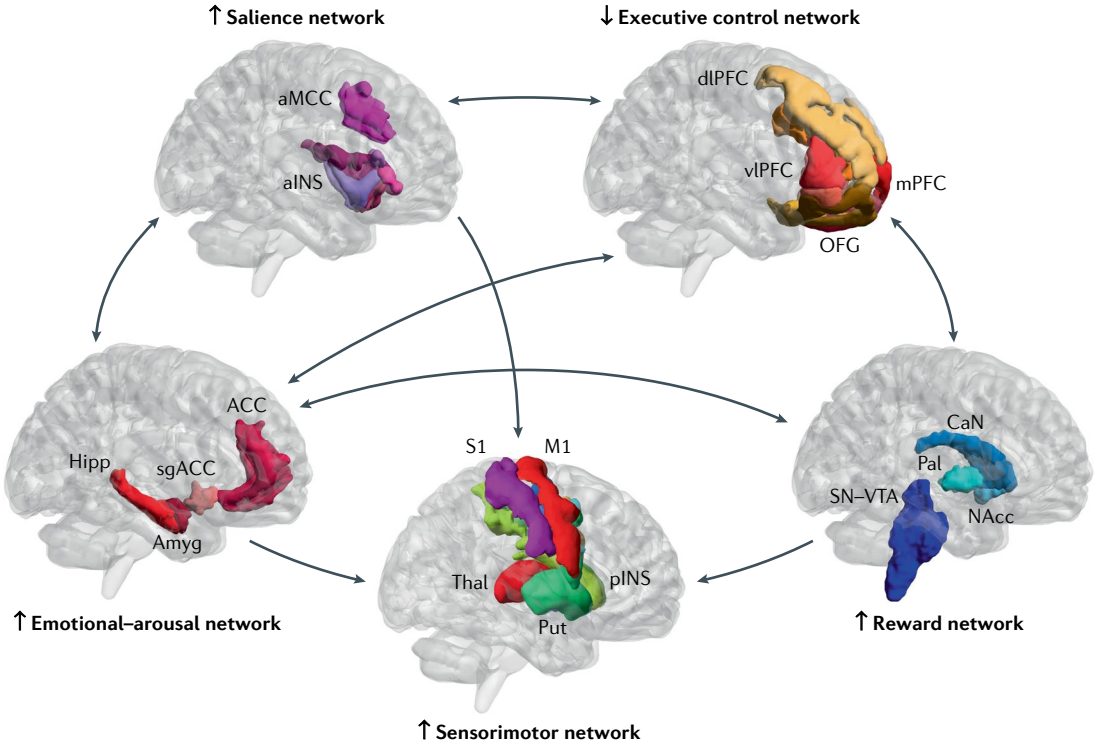

Fig. 2 | **Model of altered brain network interactions in food addiction.** Several brain networks interact in the regulation of ingestive behaviour. In food addiction, increased engagement of the salience network by food cues engages the executive control network leading to increased attention to food, and the emotional–arousal network. Insufficient inhibitory control of the reward network and the emotional–arousal network by the executive control network plays a key part in shifting the balance from predominantly homeostatic to hedonic and in regulation of food intake. The salience network 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, behavioural, affective and visceral autonomic responses to such stimuli. The executive control network 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 network and the reward network. The reward network 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 sensorimotor network receives sensory input from the body, and is important for awareness of body sensations and the generation of appropriate motor responses and behaviours. The emotional–arousal network is activated by perceived or real perturbation of homeostasis. Arrows between brain networks indicate reported bidirectional network interactions. Arrows next to brain networks indicate reported upregulation and downregulation of the individual networks during food addiction. ACC, anterior cingulate cortex; aINS, anterior insula; aMCC, anterior mid-cingulate cortex; Amyg, amygdala; CaN, caudate nucleus; dlPFC, dorsolateral prefrontal cortex; Hipp, hippocampus; M1, primary motor cortex; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; OFG, orbitofrontal gyrus; Pal, pallidum; pINS, posterior insula; Put, putamen; S1, primary sensory cortex; sgACC, subgenual anterior cingulate cortex; SN–VTA, substantia nigra–ventral tegmental area; Thal, thalamus; vlPFC, ventrolateral prefrontal cortex.

and cognitive modulation to generate appropriate motor responses and adaptive eating behaviours[85].

Hedonic system. Individuals with obesity and with food addiction are more likely than individuals who are lean or have obesity without food addiction to display a heightened motivation to eat highly palatable foods and consume more calories from fat and protein, and have at least a 20% prevalence of comorbid conditions, such as depression, binge eating and decreased quality of life functioning, beyond those observed with obesity alone[116–119]. The closely regulated balance between hedonic and homeostatic aspects of ingestive behaviour can be altered when normal inhibitory regulation of the reward system is compromised via decreased modulation or connectivity, resulting in over-consumption of food. There are similarities between food addiction and other addictive behaviours, 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 over-consumption[32,48]. Studies in both humans and animals have shown that increased cravings and food addiction behaviours result in increased

Corticostriatal communication
The extensive communication network between the cortex, which houses the extended reward network (including the frontal cortex and insula) and the striatum, which houses the core reward network (nucleus accumbens, basal ganglia).

conditioning and motivation to seek these highly palatable foods, and these behaviours are based on alterations in regions within the extended reward network[31,33,124,125].

Evidence also exists suggesting that, similar to other addiction-like behaviours, food addiction is associated with a reduced response of the reward network to food[126]. For example, ingestion of rewarding foods or drugs leads to reduced dopamine signalling within the reward system in both individuals with obesity and those with drug addiction[127], suggesting that a reduction in dopamine signalling (as a result of both the reduced release of dopamine and the downregulation of dopamine receptors) might contribute to the over-consumption 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 serotonin (5-HT), enkephalins and GABA[131]. To compensate for this dopamine deficiency, it has been suggested that affected individuals will engage in behaviours that stimulate the brain's compromised production and utilization of dopamine, such as by the over-consumption 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]. Stress-induced eating usually depends on a number of factors such as the duration 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]. During stress, increased cortisol levels could contribute to increased gluconeogenesis, upregulation of CRF in the amygdala and other affective 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 are higher in those with obesity or who have overweight than in lean individuals[140]. A study performed in obese rats demonstrated downregulation of striatal dopamine D2 receptors compared with lean rats, similar to the findings of previous studies in humans addicted to drugs[141,142]. Furthermore, D2 receptor knockdown mice rapidly develop compulsive-like food-seeking behaviour when high-fat food is readily available[141].

Even though dopamine has been the most thoroughly investigated signalling system in addictive behaviours, several neurotransmitters other than dopamine and neuropeptides are involved in the homeostatic regulation of food intake (including orexin, leptin and ghrelin, and CRF) and have also been implicated in the rewarding effects of food, cannabinoids, opioids and 5-HT[48]. Moreover, neurons in the ventral tegmental area and/or the nucleus accumbens express GLP1, ghrelin, leptin, insulin, orexin and melanocortin receptors, suggesting that these hormones or peptides can influence the reward responses to food[48]. Rats that are fed a diet high in saturated fats and refined sugars for 2 months demonstrate reduced hippocampal brain-derived neurotrophic factor, with a concomitant reduction in synaptic plasticity[143].

Food addiction pathological mechanisms

The first 1,000 days of life are a crucial developmental period for the gut-associated immune system and the BGM axis[23,144,145]. Preclinical models of myelination and brain development suggest that the early-life microbiome regulates myelination of the prefrontal cortex[146] and facilitates proper striatal synapse function[147]. Additionally, commensal microorganisms might also have a role in programming the HPA axis for stress responses[148], a system implicated in obesity and food addiction behaviour[149–152], whereby excess cortisol and related steroids, such as those from a disrupted HPA axis, can drive adipogenesis[153] and increase food cravings[151]. Early-life exposure to different microorganisms, antibiotics, dietary factors and stress shape the relative abundance and richness of the gut microbiota, influence the immune system and brain development, modulate microbial communication with the CNS and programme maladaptive BGM interactions[8,154,155]. Although these interactions and their roles in the development of obesity have been well described[8,154,155] (FIG. 3), their links with maladaptive eating behaviour 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 neonatal 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[156]. 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[157]. 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[156–158]. 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 the trimester in which the bereavement occurred[159]. In mice, moderate maternal stress during pregnancy was found to influence postnatal brain development and gene expression in the paraventricular nucleus of

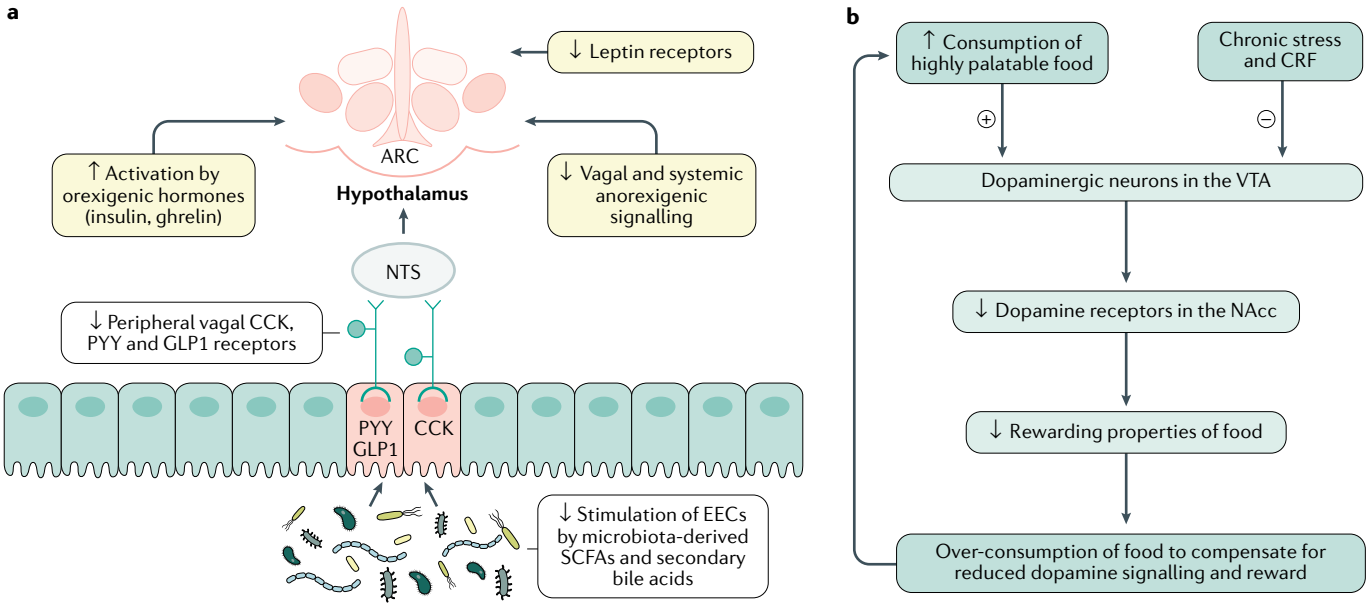

Fig. 3 | **Mechanisms in the homeostatic and hedonic systems leading to food addiction. a** | Diet-induced disinhibition of vagal and hypothalamic satiety mechanisms. A high-fat, low-fibre diet reduces the release of satiety hormones (glucagon-like peptide 1 (GLP1), peptide YY (PYY), cholecystokinin (CCK)) from enteroendocrine cells (EECs) in the gut by dietary fibre-derived short-chain fatty acids (SCFAs), leading to downregulation of receptors for satiety hormone molecules on vagal afferents innervating the EECs, and to downregulation of the vagal-mediated satiety signalling via the nucleus tractus solitarius (NTS) 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 orexigenic signals (ghrelin, insulin, cortisol). Thus, chronic exposure to a high-fat, low-fibre diet downregulates the inhibitory mechanisms of homeostatic regulation of ingestive behaviours. **b** | Diet-induced changes in the extended reward system. According to the dopamine deficiency hypothesis, a reduction in dopaminergic stimulation of neurons in the nucleus accumbens (NAcc) as a result of reduced dopamine release from the ventral tegmental area (VTA), and downregulation of dopamine receptors on NAcc neurons, reduces the rewarding effects of ingested foods, and leads to craving and over-consumption of unhealthy food in an attempt to compensate for the reduced dopamine signalling. Chronic stress-induced release of corticotropin-releasing factor (CRF) and glucocorticoid levels also have an inhibitory effect on dopamine signalling. Upward arrows and downward arrows inside boxes indicate reported upregulation and downregulation of respective mechanisms.

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[160]. As maternal antibiotic use during the second or third trimester was associated with an increased risk of obesity in the offspring regardless of pre-gravid BMI in a study of 436 mother–child dyads[161], and the vaginal microbiota plays an important part in shaping the infant microbiome, as demonstrated in a very well-characterized group of nine mothers and their ten newborns[162], 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[163]. The limited bioavailability of HMOs in the small intestine enables efficient delivery to the developing infant gut microbiota, most notably *Bifidobacterium*, which can degrade these sugars[163]. Exclusively breastfed infants showed a more diverse *Bifidobacterium* microbiota (175 faecal samples from seven infants) than exclusively formula-fed infants (154 faecal samples from seven infants), which might set the stage for future, beneficial BGM interactions[164] given that a robust *Bifidobacterium* community has been shown to be protective against intestinal infections[165] and associated with appropriate development of the infant immune system[166]. Limited data exist on the effect of combination feeding (breastmilk and formula) on the gut microbiome, despite how common it is[167]. Bogen et al.[168], in an observational study of more than 70,000 infants, found 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 (OR 0.70 for developing obesity, 95% CI 0.61–0.81) to exclusive breastfeeding for 16–26 weeks (OR 0.71, 95% CI 0.56–0.92).

The relative abundance 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 abundance of

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

Bacteroidetes and elevated SCFA levels, as suggested by a high-quality, 2.5-year case study of 60 faecal samples from a single infant[169]. However, in a study in 1,087 infants, the faecal microbiota profile assessed at 3 months of age (composed of primarily Bacteroidaceae, Bifidobacteriaceae, Enterobacteriaceae, Lachnospiraceae, Ruminococcaceae, and Veillonellaceae) was a more reliable predictor of future risk of having overweight than querying the microbiota profile at 12 months[170]. 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[171].

Highly processed foods, which contain large amounts of salt, sugar, fat and additives, have become increasingly available in the developed world[172,173]. A pattern of increased exposure and ingestion of such foods in childhood might programme food preferences and increase the risk of developing food addiction into adulthood[174]. Additionally, the relentless marketing of such foods, starting in childhood, has contributed to the increased uncontrollable consumption of and cravings for unhealthy foods, especially in children[175,176].

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[177]. In a US cohort 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)[178]. In a longitudinal study in 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[179]. 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 having overweight at 7 years in children from normal weight mothers, but not in those from mothers with overweight; the gut microbiota of study participants were not examined in this study[180]. Although it is difficult to draw definitive conclusions from natural history and cross-sectional epidemiological studies, numerous preclinical studies[181–184] 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[181]. Another study in mice 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 $CD4^+$ $IL\text{-}17A^+$ lymphocytes in the small intestine, decreased IgA secretion in the intestine)[185]. 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 whether and how antibiotic-induced microbiome alterations can influence the brain and alter ingestive behaviours.

Early adversity. A history of early adverse life events (EALs), such as natural disaster, parents divorcing, emotional or physical abuse, or sickness or death of a family member, predispose individuals to develop obesity and food addiction in adulthood, mainly through mechanisms associated with stress, inflammation, emotional perturbations, maladaptive coping responses and metabolic disturbances[186,187]. 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; $P < 0.001$)[188–190]. Preclinical models of early adversity (maternal separation model) have shown that addictive behaviours can develop later in life, but the effects of early adversity require further investigation in humans, especially as the underlying mechanisms are unknown and these animal models are poor models of human behaviour[191]. For example, rats exposed to limited nesting stress in the postnatal period had an immature HPA axis, which was associated with reduced gut microbiota diversity, with an especially notable reduction in bacteria capable of degrading fibre[192]. Although the causal relationship between adversity during childhood and adult obesity is incompletely understood, it has been suggested that over-consumption of highly palatable foods even when hunger has been satisfied to satiety is a possible coping mechanism to deal with the increased stress responsiveness seen in individuals with a history of EALs[193–196]. 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[197]. 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 than in women[197]. For example, compared with men, women show increased postprandial activation in the brain's reward regions, which might increase susceptibility to cravings for highly palatable foods and result in hyperphagia[198,199]. Although the exact molecular mechanisms by which women, compared with men, experience this increased susceptibility remain unclear, results from a pilot study in 63 individuals with varying BMI levels suggest that EALs might contribute to the development of food addiction by interfering with BGM interactions, specifically microbial tryptophan metabolism and reward brain regions such as the amygdala, anterior insula and nucleus accumbens[200].

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

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-calorie and palatable food is abundant in the developed world[201]. Studies have shown not only that enhancement of the taste and salience of food increases cravings and ingestion of the food, but also that contextual factors such as stress can serve as conditional cues for future food intake and long-term weight gain[125,202,203]. In fact, over-consumption of highly palatable food, in particular food containing high levels of fat and sugar, reduces the reward thresholds of the food when ingested because of reduced levels of dopamine and dopamine receptors in the brain, and therefore leads to the need for increased intake of such food to generate the same satisfaction[204,205]. Although long-term ingestion of such highly palatable food has been shown to alter gut microbial diversity and relative abundance 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 in 98 individuals[206,207].

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[208]. Food labels and plate and utensil sizes can moderate the portion control effect by increasing food intake[209]. 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[210–213]. In a study of more than 46,000 adults, individuals with obesity also reported an increased preference and craving for foods rich in fat and sugar[214].

Psychosocial stress. Psychosocial stress can also stimulate ingestive behaviour in adults by increasing appetite, cravings and motivation to consume highly palatable foods, thereby contributing to stress-related weight gain in obesity[125,215,216]. In individuals with obesity, strong associations have been shown between perceived stress and food addiction, snacking, cravings and abnormal eating patterns[124,217]. For example, a study in 339 adults (mean ± s.d. BMI 26.7 ± 5.4 kg/m^2) demonstrated that chronic stress can influence levels of the orexigenic hormone insulin, as well as glucose and cortisol responses, which in turn can lead to increased food intake and weight gain[218]. Paradoxically, although the ingestion of 'comfort food' high in fat and sugar can reduce subjectively perceived stress, various studies have shown that ingestion of such food 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 behaviours[132,219–221].

In a mouse model, chronic psychosocial stress resulted in a global reduction in gut microbiota richness and diversity, including a reduction in the relative abundance of *Akkermansia*[222], which has been indicated in previous investigations to have beneficial effects within the context of human obesity and metabolic syndrome[223]. 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[222]. These changes might have been mediated, at least in part, by alterations in immunoregulatory signals, as these mice showed transient elevations in the number of IL-10$^+$ T regulatory (T_{reg}) cells, which were suppressed over time[222].

Amino acid metabolites. Tryptophan and its metabolites — 5-HT, kynurenine and indole — have been implicated as important mediators of BGM interactions within the context of obesity and food addiction[224,225]. Of these metabolites, the most extensively studied is 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)[226]. Of the body's 5-HT, 95% is stored in gastrointestinal ECCs, and the gut microbiota, through the production of SCFAs and secondary bile acids, can regulate 5-HT synthesis and its release from ECCs[227–229]. A review of studies in humans involving acute tryptophan depletion (typically by providing individuals with a large protein load containing non-tryptophan 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, underscored the effect of changes in 5-HT release on food preference[230]. In a study of 55 women following acute tryptophan depletion, participants who had overweight showed a statistically significant increase in sweet calorie intake and preference for sweet foods compared with a placebo intervention[231]. By contrast, the lean group showed no differences, suggesting that individuals who have overweight might be more susceptible to changes in tryptophan metabolism and 5-HT availability[231]. Host and microbial cells 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[232].

Although 5-HT has been the most extensively studied tryptophan metabolite, the majority of tryptophan is converted by host cells to kynurenine[233]. In the gastrointestinal tract, kynurenine is synthesized from tryptophan by the rate-limiting enzyme indoleamine-2,3-dioxygenase, which can be upregulated by inflammatory cytokines or downregulated by reactive oxygen species such as hydrogen peroxide produced by intestinal *Lactobacillus*[234,235]. 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[236]. Alternatively, increased flux through the kynurenine pathway can influence the brain through neuroactive downstream metabolites such as kynurenate and quinolinate,

Psychosocial stress
Stress originating from the environment that is sufficient to cause dysregulation of homeostatic responses and physical or psychological symptoms.

Perceived stress
Stress from events in an individual's life perceived as stressful. The most widely used scale for perceived stress is the Perceived Stress Scale.

which function as an *N*-methyl-D-aspartate (NMDA) antagonist and an NMDA excitotoxin or neurotoxin, respectively[234]. 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[237].

Another important group of tryptophan metabolites is the indoles. Most undigested dietary tryptophan in the gut lumen is converted exclusively by gut microorganisms to indole[238]. In studies in animals and humans, 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[239], all of which have been shown to be disrupted in states of obesity[237,240–242]. 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 behaviours, with regions of the extended reward network (nucleus accumbens, amygdala and anterior insula) playing an important part in this interaction[200].

Metabolic endotoxaemia. In mouse models of obesity, a diet high in fat (60% lard) and low in dietary fibre has been implicated in long-term disruption in gut microbiota diversity[243], whereas diets high in fibre result in positive alterations in ingestive behaviour (decreased food intake, increased satiety)[244]. When dietary fibre is reduced or unavailable, certain gut microorganisms such as *Akkermansia muciniphila* consume the glycans making up mucins in the mucus layer of the gut, thereby compromising intestinal barrier function[245]. This phenomenon is referred to as increased 'leakiness' of the gut (FIG. 4). Sonnenburg et al.[243] 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[243]. Remarkably, supplementation with a high-fibre diet alone was insufficient to normalize microbial diversity[243]. 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[246–249].

The combination of a leaky gut and an over-abundance of inflammatory bacterial products is thought to result in elevated plasma levels of LPS and pro-inflammatory cytokines, including IL-1β, IL-6 and TNF[250]. Increased systemic immune activation can shift tryptophan metabolism towards the kynurenine pathway and away from 5-HT or indole synthesis, as described previously[251]. 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[252–254], and by reducing the expression of anorexigenic

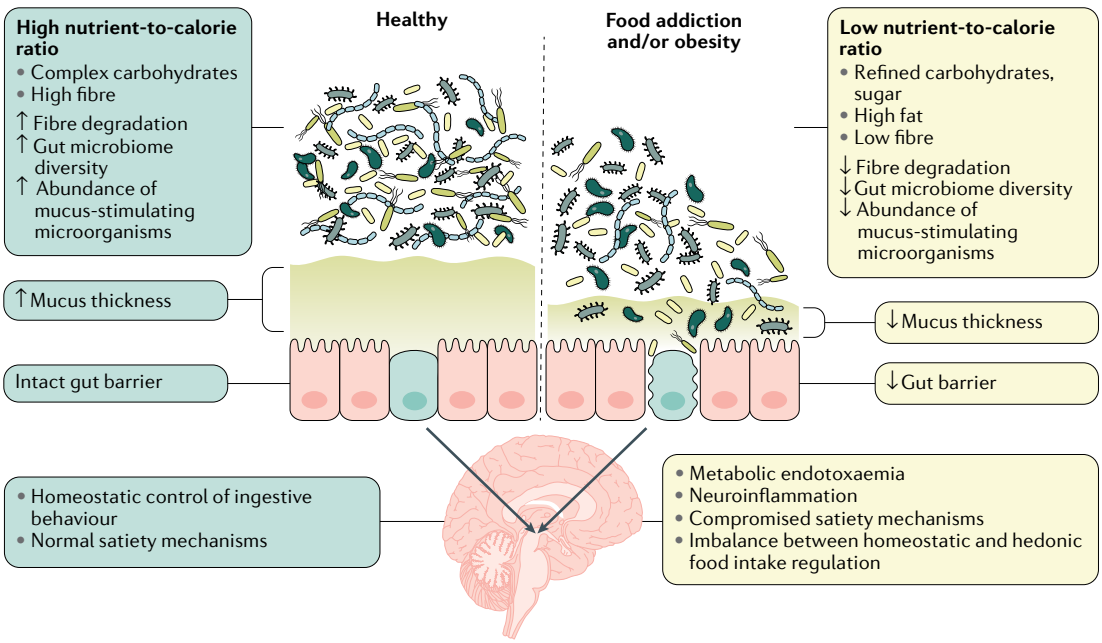

Fig. 4 | **Interactions between food, gut microbiota and intestinal permeability in the regulation of ingestive behaviour.** Left: a healthy diet (high in fibre, low in fat and sugar) is associated with a high diversity of the gut microbiota, including an abundance of taxa involved in stimulating mucus production in humans and animal models. The combination of an intact mucus layer and tight intestinal epithelium results in an intact gut barrier. Right: an unhealthy diet (high in fat and sugar, low in fibre) is associated with a reduced microbial diversity, a reduction in mucus-stimulating microorganisms, a 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 over-abundance of inflammatory bacterial products is thought to result in elevated plasma levels of LPS and pro-inflammatory cytokines. This state of metabolic endotoxaemia has been shown to reduce central satiety mechanisms by influencing enteroendocrine secretion of the satiety hormones peptide YY, cholecystokinin and serotonin, and by reducing the expression of anorexigenic peptide receptors and leptin receptors on vagal afferents and in the hypothalamus, respectively, leading to disinhibition of satiety mechanisms. Adapted with permission from REF.[323], Wiley.

Box 1 | Therapeutic targets within the brain–gut–microbiome axis for obesity

Approaches to obesity treatment:

- Cognitive control
  - Cognitive behavioural therapy
- Reward processes
  - Topiramate plus phentermine
  - Bupropion plus naltrexone
  - GLP1 agonists (e.g. liraglutide)
- Homeostatic control
  - Serotonin modulators (e.g. lorcaserin)
  - Amphetamines (e.g. phentermine)
  - GLP1 agonists (e.g. liraglutide)
  - Leptin agonists
  - Vagus nerve electrical modulation
- Gut remodelling
  - Bariatric surgery (e.g. RYGB or LSG)
  - Bariatric endoscopy (e.g. gastric balloons, gastric plication, gastric content aspiration)
- Gut absorption
  - Lipase inhibitors (e.g. orlistat)
  - Mucosal ablation (e.g. duodenal sleeve)
- Gut microbiota
  - Prebiotics (e.g. oligofructose, oligosaccharides)
  - Probiotics (e.g. *Lactobacillus*)
  - Bariatric surgery
  - Faecal microbiota transplantation

GLP1, glucagon-like peptide 1; LSG, laparoscopic sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass

peptide receptors and leptin receptors on vagal afferents[255] and in the hypothalamus, respectively[256]. 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[257]. In addition to changes in ingestive behaviour, there are probably numerous other mechanisms contributing to high-fat diet-induced obesity, such as gut microbiota-driven remodelling of the intestinal transcriptome to favour an obesogenic signalling cascade[258].

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 fibre that preferentially increases gut *Bifidobacterium* abundance, showed reduced endotoxaemia, decreased levels of plasma and adipose tissue pro-inflammatory cytokines, and improved glucose tolerance[259]. In this study, no relationship was seen between endotoxaemia and any bacterial group other than *Bifidobacterium*[259]. 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 endotoxaemia perpetuate these maladaptive changes at all levels of the BGM axis (FIG. 1).

Clinical implications of food addiction

The proposed systems biology model of altered BGM interactions resulting in maladaptive changes in ingestive behaviour provides not only a plausible explanation for the refractory nature of obesity to many traditional therapeutic strategies, but also a rationale for several new therapeutic strategies (BOX 1; FIG. 5).

Gut-directed therapies

As the gut is the primary source of hunger and satiety signals that regulate homeostatic feeding behaviours, it is not surprising that several obesity treatments, including bariatric surgery, aim to modify these gut mechanisms. Most 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[260,261]. 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[262–264], which predicts long-term weight loss outcomes[265–267]. Evidence also exists for the role of bariatric surgery-induced weight loss in driving remission of food addiction (as assessed using the YFAS); one study in 14 patients with obesity and with food addiction prior to surgery demonstrated remission of food addiction in 93% following surgery-induced weight loss ($P < 0.001$)[268]. 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[262,264].

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[262,269–271]. 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 signalling, and increased production of SCFAs[272–276]. Preliminary work in individuals with obesity undergoing bariatric surgery has suggested that changes in gut microbiome composition and microbial metabolism of aromatic amino acids and glutamate are associated with reductions in appetite, food addiction and changes in food preferences, suggesting a possible causal role of these metabolites in behavioural responses[277–282]. 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[283]. As discussed above, this anti-inflammatory effect could increase hypothalamic sensitivity to satiety signals and to insulin, resulting in a shift towards more homeostatic regulation of ingestive behaviours[284–289]. 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[290].

Microbiome-directed therapies

Microbiome-directed therapies, including faecal microbiota transplantation (FMT), are novel therapeutic options for obesity and metabolic syndrome. In small clinical studies (one study including 18 individuals, 9 receiving autologous FMT and 9 receiving allogenic FMT from a lean donor, and another study including 38 individuals, 12 receiving autologous FMT, 26 receiving

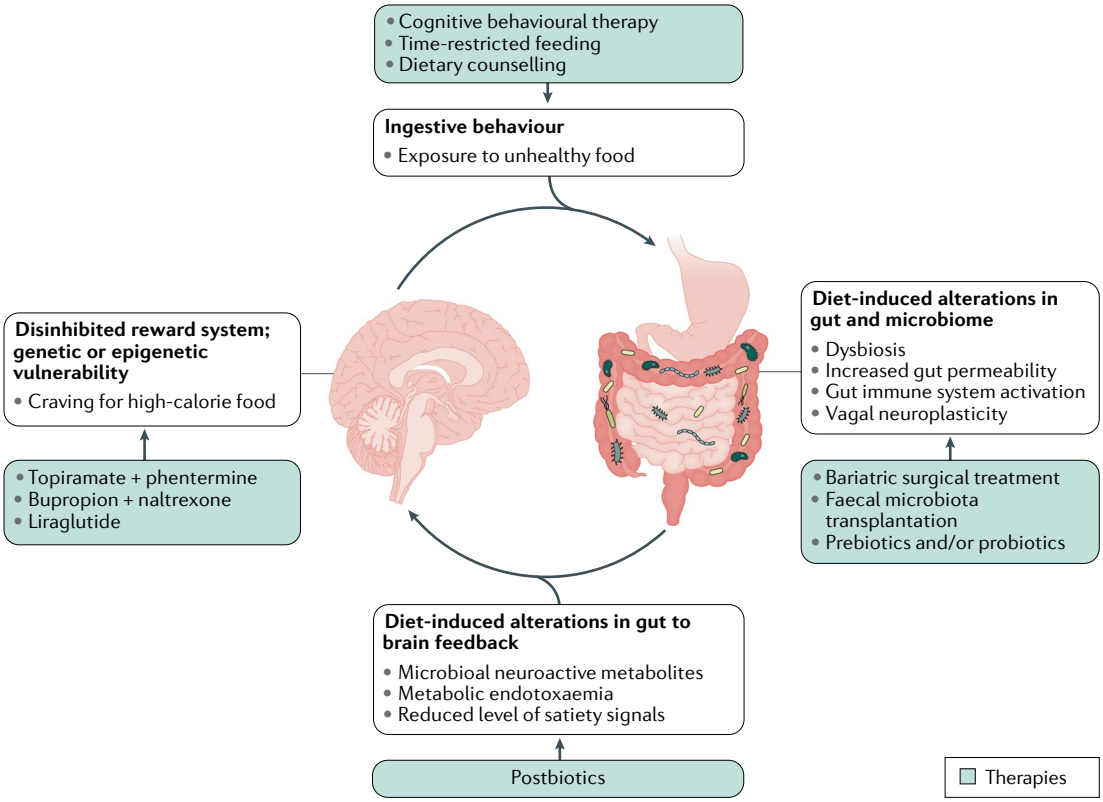

Fig. 5 | **Circular model of brain–gut–microbiome interactions in obesity and targets for intervention.** The interaction of genetic and epigenetic factors influences the balance between hedonic and homeostatic control of ingestive behaviour, and the risk for the development of hedonic dominance. When exposed to ubiquitous food high in calories (fat, sugar) and low in fibre, predisposed individuals will over-consume such foods, resulting in changes in the gut and the microbiome as shown in FIG. 3. The resulting change in gut–brain signalling can further compromise homeostatic regulation of food intake and reinforce the disinhibition of the reward system. Targets for intervention and therapeutic modalities include: altering ingestive behaviour (for example, cognitive behavioural therapy, time-restricted eating or dietary counselling); alterations in the gut and microbiome (for example, bariatric endoscopic and surgical treatment, faecal microbiota transplantation or prebiotics and/or probiotics); altering gut–brain feedback (postbiotics such as butyrate, tryptophan-derived compounds including indoles and other amino acid metabolites); and altering the reward system (centrally acting medications).

allogenic FMT from a lean donor), FMT from lean donors resulted in increases in butyrate-producing bacteria and improved insulin sensitivity in recipients with metabolic syndrome[291,292]. The improved insulin sensitivity and associated changes in the faecal microbiome were not sustained at 18 weeks, suggesting a resilient faecal core microbiome[292]. 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[292]. Ingestive behaviours were not assessed in those studies. It is well known that microbial products such as SCFAs modulate feeding behaviour via central mechanisms[19]. For example, in a study of 20 healthy men without obesity, the intake of a type of fibre that selectively increases gut microbial propionate production was associated with lowering the subjective appeal of, and the brain reward activation (as measured by brain MRI) in response to, pictures of highly palatable food[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 and changes in bowel habit[293].

Time-restricted eating

Interest is increasing in the potential benefits of different types of time-restricted eating, including intermittent feeding and the fasting mimicking diet, in reducing obesity and improving cardiovascular health and health during ageing[294–296]. In mice, ad libitum exposure to a high-fat diet resulted in changes in circadian rhythms and feeding behaviours that led to increased energy intake and weight gain[297]. These changes could be reversed by time-restricted feeding[298]. One study showed that in individuals who had overweight but were otherwise healthy, adhering to time-restricted eating 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 behavioural change resulted in sustained weight loss up to 1 year after the intervention[299]. The role that the microbiome plays in mediating the effects of time-restricted eating in humans is not known. However, in animals 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[300]. 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 behaviours leading to compromised oscillations have been associated with obesity and metabolic syndrome[301]. There are other potential factors that might contribute to the benefits of time-restricted eating, 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[302–304]. Of the medications now available for weight loss in the USA, some decrease appetite by directly affecting the hypothalamus (phentermine, bupropion, naltrexone and lorcaserin), and/or modulating reward circuits in the brain (naltrexone, bupropion and 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[305–308]. A dual effect, reducing appetite and reward-based eating, is achieved through the use of hormonal satiety signals, such as GLP1 agonists (liraglutide or exenatide)[277,309]. Very little is known about the effects of these anti-obesity medications on the gut microbiota. In a small study in 19 individuals with type 2 diabetes mellitus, treatment with liraglutide for 42 days resulted in a statistically significant increase in the relative abundance of the genus *Akkermansia*[310].

Cognitive behavioural therapy (CBT) in individuals with obesity and food addiction aims to change specific thoughts, beliefs and cognition directly related to the feelings and behaviours attributed to uncontrollable ingestive behaviours and cravings[311,312]. Since CBT strengthens prefrontal control mechanisms[313–318], 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[319–322].

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. However, 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 signalling within the BGM axis, it is unlikely that a single microbial metabolite could causally explain the behavioural 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 behaviour in humans, such as bariatric surgery, time-restricted eating and CBT, are needed to probe for a causal role of the gut microbiome. Such studies in humans should be combined with reverse translational studies, evaluating the effect of FMT on rodent feeding behaviours and body weight.

Conclusions

Altered BGM interactions manifesting as dysregulated eating behaviour and resulting in obesity can best be understood as a complex, circular system that is stable and highly resistant to change (FIG. 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-calorie foods reinforcing the gut dysbiosis (FIG. 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 (FIG. 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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Competing interests
E.A.M. serves on the scientific advisory boards of Amare, APC Microbiome Ireland, Axial Biotherapeutics, Bloom Science, Danone, Mahana Therapeutics, Pendulum and Viome. A.G. and V.O. declare no competing interests.

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