Trends in Cognitive Sciences

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REVIEWS

Review

The Prefrontal Cortex and Obesity: A Health Neuroscience Perspective

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In the modern obesogenic environment, limiting calorie-dense food consumption is partially dependent on the capacity of individuals to override visceral reactions to hyperpalatable and rewarding food cues. In the current review, we employ a health neuroscience framework to outline: (i) how individual variations in prefrontal cortical structure and functionality, and by extension, executive functions, may predispose an individual to the overconsumption of appetitive calorie-dense foods via differences in dietary self-regulation; (ii) how obesity may result in changes to cortical structure and functionality; and (iii) how the relationship between the structure and function of the prefrontal cortex and obesity may be best described as reciprocal in nature.

Highlights

In this review, we use a health neuroscience framework to highlight the potential reciprocal relationship between obesity and the prefrontal cortex (PFC). Specifically, we outline how the PFC can be viewed as a predictor, a mediator or causal agent, moderator, or outcome of obesity.

In the modern environment, dietary self-regulation is especially dependent on the capacity of the PFC to exert modulatory control over food choices. Weaker modulation increases the likelihood that individuals will overconsume appetitive calorie-dense foods.

Over time, the persistent and sustained overconsumption of calorie-dense foods can lead to weight gain and, subsequently, obesity.

Diet-evoked obesity can lead to marked and enduring changes in cognitive control and PFC functionality, which, in turn, drives the maintenance of unhealthy eating behaviours.

The Prefrontal Cortex and Obesity

In recent years, data derived from neuroimaging and cognitive assessments have been used to explain how specific patterns of brain responsivity interact with the modern obesogenic environment to modulate individual's susceptibility to overconsumption and, subsequently, weight-gain and obesity. The excessive consumption of highly palatable calorie-dense foods (i.e., those laden in sugar and refined fats) is thought to be a primary factor contributing to the development of obesity [1]. Specifically, there is a growing consensus that a shared behavioural and neurobiological phenotype underlies obesity and addiction (Box 1), and this phenotype can be used to explain individual vulnerability to obesity in the modern environment. However, the prominent neurobehavioural models of obesity overemphasise dysregulation of the mesocorticolimbic reward system and heightened responsiveness to food cues as the crucial precursor to overconsumption and downplay the contribution of other brain regions, specifically, the **prefrontal cortex (PFC)** (see Glossary).

In the current review, we use a health neuroscience framework [2] to provide a comprehensive model centring on PFC function as a critical factor for an individual's vulnerability to obesity. Under this framework, the brain can be conceptualised as either a primary determinant that mediates physical health through 'top-down' regulation of behaviours, or as a target organ that is affected by health behaviours and physical health through 'bottom-up' pathways (see [2] for an overview). As such, the brain can be viewed as a predictor, a mediator or causal agent, moderator, or outcome (dependent variable) of a health behaviour(s). This framework differs from past comprehensive reviews, which have focused primarily on **executive functions** as a predictor of eating behaviour [3–5].

Specifically, in this review we explore: (i) how individual differences in the functional and structural integrity of the PFC, including grey matter volume and functional activation during food choice decisions, and underlying cognitive processes (i.e., executive functions) may predispose an individual to obesity via individual differences in dietary self-regulatory abilities (i.e., the capacity to exert conscious control over food choice); (ii) how the chronic consumption

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of calorie-dense foods modulates both reward sensitivity and PFC functionality, resulting in the observed neurocognitive deficits apparent in persons with obesity; (iii) and we outline a potential model that highlights the reciprocal relationship between obesity and brain health, as mediated by calorie-dense food consumption. The mechanistic insights provided within the current review will bridge current neurobehavioural models and assist in defining the neurobiological processes underpinning food choice and the control of eating behaviours, paving the way towards the development of brain-based preventative strategies and interventions aimed at reducing the prevalence of obesity worldwide.

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PFC Function as a Predictive Biomarker of Obesogenic Eating Behaviours

Researchers are increasingly beginning to recognise the utility of using neuroscientific data as a means of identifying potential brain biomarkers that can predict future health outcomes and behaviours; past research has focused primarily on the brain as an outcome variable. An important caveat of this approach is the use of structural and functional data to predict individual differences in the engagement and maintenance of health behaviours. Within the context of obesity, this would entail the identification of certain brain characteristics that can predict obesity susceptibility, as driven by the persistent and sustained overconsumption of calorie-dense foods.

Humans have a strong and reliable preference for foods that are high in fat and sugar, a preference that is thought to be rooted in longstanding evolutionary demands [6,7], making the detection and ingestion of such foods the preferential or default choice. This is coupled with a modern environment saturated with an abundance of hyperpalatable calorie-dense foods and ubiquitous consumptive cues (e.g., media advertisements). The exposure to both palatable food and food cues can induce excessive food cravings and the tendency to overindulge in the absence of physiological hunger [8]. As such, in the modern environment, dietary self-

Box 1. Current Neurobehavioural Models of Obesity

Several excellent and comprehensive review papers outlining the reward-centred neurobehavioural models of obesity exist (see [79,80]). As such, the premises underlying these models are briefly outlined here to draw comparisons and identify the gaps that can be addressed using a PFC model of obesity. The exposure to appetitive food images and cues, and the anticipated and actual intake of palatable calorie-dense foods increases cortical activity in the regions associated with reward processing and incentive valuation, including the ventral striatum, midbrain, amygdala, and the OFC [79,80]. The incentive sensitisation theory of obesity posits that such reward-related cortical responsivity to high-caloric foods predisposes an individual to obesity by putatively overriding homeostatic processes, resulting in the subsequent overindulgence in calorie-dense foods [79,80]. Consistent with this notion, in comparison with healthy weight controls, persons with obesity show elevated cortical activity within these reward-regions, including the OFC, amygdala, and ventral striatum, in response to calorie-dense food stimuli [81–85]. This pattern of activation is similar to that observed in drug users and abusers [86] and has led to the concepulatision of the food-addiction models of obesity [87]. Notably, baseline levels of activation in response to hyperpalatable food cues within these regions is associated with body weight and BMI [88], and is predictive of weight gain in adults and adolescents up to 3 years later [89,90].

Conversely, the reward deficit models posit that overeating is a function of lower dopaminergic signalling with the mesolimbic reward-regions. As such, persons with obesity overeat to compensate for this deficiency [91,92]. This is supported by studies demonstrating that dopamine binding to dopamine D2 receptors (D2R) is decreased in the ventral striatum of obese individuals, indicating downregulation of D2R [93]. These observations are complemented by the observation that the *Taq*IA A1 allele genetic polymorphism results in decreased striatal D2R density, and those with this allele have an increased incidence of obesity [94]. However, the reward deficiency model, within the context of food-related human neuroimaging work, has been recently challenged. Instead, it has been proposed that heightened striatal responses to food cues and attenuated responses to the receipt of palatable food reflects the encoding of reward-related learning signals linking reward expectations to consumption (see [95] for an overview).

Recent advances have attempted to synthesise the incentive sensitisation theory and reward deficiency theories into the dynamic vulnerability model of obesity (see [80] for an overview).

regulation is especially dependent on the capacity to suppress automaticity in eating behaviours evoked by appetitive food stimuli [3–5]. The ability to override or inhibit such visceral responses to food cues (i.e., exert dietary self-regulation) varies substantially among individuals, suggesting that individual differences in the structure and function of the cortical networks that support behavioural regulation (i.e., the PFC) may predict individual vulnerability to overconsumption. A large body of literature supports this notion, with several observational studies demonstrating that the tendency to overconsume calorie-dense foods is stronger in individuals with weaker inhibitory control [9–12], and this effect is amplified when environmental cues encourage consumption [13,14].

Neuroimaging techniques have allowed the extension of these behavioural studies by linking functional activation and the structural integrity of the underlying cortical regions and networks, specifically the dorsolateral PFC (dlPFC), to food choice-related self-control and cognitive control over appetitive food cravings [15,16]. For instance, evidence from **fMRI** studies have shown that weaker functional coupling between the dlPFC and ventromedial PFC (vmPFC) reduces the capacity of the dlPFC to downregulate taste attributes within the vmPFC, increasing the likelihood that individuals will select food items on the basis of taste compared with healthiness [15], indicating that dietary self-regulatory success may be dependent on the capacity of the dlPFC to modulate taste and health valuations in the vmPFC. Recent work has expanded on these findings by demonstrating that, when presented with appetitive calorie-dense food images, increased blood-oxygen-level dependent (BOLD) responses in the dlPFC and inferior frontal gyrus (IFG) were observed when participants were instructed to supress food cravings and the motivation to eat [16–18]. Additionally, grey matter morphometry has also been shown to modulate dietary self-regulation, in that increased regional grey matter volumes within the dlPFC and vmPFC were shown to be positively associated with dietary self-regulatory success [19].

Specifically, the recruitment of the dlPFC is proposed to be necessary to implement the appropriate cognitive strategies necessary to suppress or dampen food-evoked visceral cravings [16]; see Box 2 for a description of the underlying mechanisms. Indeed, overlapping patterns of cortical activity within the brain regions typically associated with cognitive control and emotion regulation are observed when participants are instructed to regulate or suppress food cravings [20]. Specifically, when participants were instructed to regulate or suppress food cravings, increased activity in the left dlPFC, bilateral mid-cingulate cortex, and temporal parietal junction was observed [20]. This indicated that the dlPFC is a critical functional node for the downregulation of the rewarding properties of energy-dense foods, thereby enabling individuals to exert control over their consumptive behaviours. Interestingly, body mass index (BMI) was negatively associated with activation in the left dlPFC, right ventrolateral PFC (vlPFC), and IFG during the regulate conditions [20], suggesting that persons with obesity may be less able to recruit the dlPFC to modulate food choices. Together, these findings provide a convincing platform outlining how individual differences in the structural and functional integrity of the dlPFC may predispose an individual to overconsumption in the modern environment. However, the hemispheric specialisation of this effect (see Box 3 for a discussion) remains unclear.

Recently, attention has been directed towards using baseline functional activation in response to food cues and/or during executive function or reward-based decision-making paradigms as a predictor of weight gain and consumptive behaviours. For instance, functional activation in the lateral PFC during an inhibitory control [21] and food-cue exposure task [22] has been shown to be positively associated with reductions in momentary desires for hyperpalatable foods [22] and the decreased likelihood of overeating over a 1 week period [21]. These studies are especially noteworthy, as they highlight the potential for cortical activity to predict real-world

Glossary

Adiposity: adiposity is a term used to denote excess fat or obesity.
Executive functions: executive function is an overarching term used to refer those to higher-order cognitive functions, such as working memory, planning, decision-making, and inhibitory control, implicated in the 'top-down' control (i.e., non-stimulus driven control) of human behaviour [76].
fMRI: functional MRI measures changes in brain activity through the detection of changes in cerebral blood flow, either while a participant is resting (resting state fMRI) or while a participant completes a task. Blood-oxygen-level dependent (BOLD) contrasts are the primary method used in in fMRI to quantify changes in blood flow.
Noninvasive brain stimulation (NIBS): NIBS methodologies are a class of neuroscience tools that can safely modulate cortical activity in targeted neuron populations; the acute effects are temporary, lasting up to approximately 1 hour poststimulation. The effect (excitatory or inhibitory) depends on the frequency and parameters used. These methods are used in both research and clinical settings [77].
Prefrontal cortex (PFC): the most anterior part of the frontal lobes (i.e., the front part of the frontal lobes). The PFC is highly interconnected with several cortical and subcortical regions. These connections are thought to enable PFC control over human behaviours, actions, and thoughts. The PFC is one of main neuroanatomical regions involved in executive functioning or cognitive control [78].
Repetitive transcranial magnetic stimulation (rTMS): transcranial magnetic stimulation (TMS) is a NIBS technique in which a magnetic coil is placed directly on the scalp of the participant. The coil emits a small magnetic field, inducing an intracranial electrical current. This results in neuronal depolarisation and, subsequently, an action potential in those neurons under the coil. Repetitive TMS (rTMS) is a TMS variant that is used to modulate ongoing neural activity within specific cortical regions for up to 60 minutes poststimulation [77]. Conventional

Box 2. Neurobiological Correlates of Dietary Control

The cognitive control mechanisms implemented by the dlPFC are thought to work in tandem with subcortical and cortical reward-regions, most notably the ventral striatum and vmPFC to modulate reward processing and valuation; presumably by inhibiting the inappropriate responses or devaluing immediate appetitive rewards. Specifically, dlPFC modulation of dopaminergic activity in the ventral tegmental area (VTA) and nucleus accumbens (NAcc) is thought to be crucial for the integration of reward valuations and subsequent implementation of goal-directed behaviours [96]. Within the context of consumptive behaviours and food-cue responsivity, weaker dlPFC modulation of these reward-regions may predispose an individual to the overconsumption of calorie-dense foods via increased valuation of the food item in conjunction with a lower ability to control consumption.

Consistent with this notion, the cognitive and behavioural aspects of dietary self-regulation are thought to be dependent on the capacity of the dlPFC to modulate incentive valuation and reward processing within the vmPFC and ventral striatum [15,16]. For instance, the association between left dlPFC activity and the regulation of food and cigarette cravings has been shown to be directly mediated by reductions in ventral striatal activity [16]. Likewise, the induction of acute stress results in increased BOLD activity within the amygdala and ventral striatum, and enhances the functional coupling between the vmPFC, amygdala, and ventral striatum. This is coupled with weaker modulatory connections between the dlPFC and vmPFC [97]. Such decreased modulatory input from the dlPFC, in conjunction with stronger reward valuation inputs within the vmPFC and limbic regions, was thought to increase the relative weight assigned to taste attributes when selecting foods items, increasing the likelihood that stressed individuals will select food items on the basis of taste rather than healthiness or health goals [97]. These findings are noteworthy, as they demonstrate that naturalistic attenuations in dlPFC activity may predispose an individual to the overconsumption of hyperpalatable calorie-dense foods via an increase in the reward values assigned to tasty, but unhealthy, food items.

consumptive behaviours (i.e., outside of a laboratory setting). These findings are complimented by recent work demonstrating that greater functional activation in the IFG while viewing food cues was positively associated with weight loss, attributed to a calorie restriction diet, up to 3 months later [23]. The observed diet-induced weight loss was correlated with increased connectivity between the dlPFC and vmPFC, supporting the notion that dlPFC modulation of taste valuations in the vmPFC is an essential aspect underlying dietary self-regulatory success. This may be particularly true when individuals need to restrict caloric intake to achieve weight-loss goals [23]. Likewise, lower levels of functional activation within the inferior, medial, and superior frontal gyri during a delay discounting paradigm has been shown to predict postdiet weight changes up to 3 years later, independent of age and demographics [24,25]. These findings are particularly interesting, as they highlight that PFC functionality during reward-based decisions plays a crucial role in weight maintenance and weight loss efforts by enabling individuals to suppress immediate appetitive rewards in favour of long-term outcomes and goals, and that such functionality can predict obesity progression or weight gain in a similar manner as reward-region responsivity.

The PFC as a Causal Agent Underlying Obesogenic Eating Behaviours

Although an association can be drawn between the structural and functional integrity of the PFC, primarily the dlPFC, and dietary self-regulatory success, the above findings cannot inform the causal or predictive means by which PFC activity may modulate obesogenic eating behaviours. Fortunately, emerging evidence using **noninvasive brain stimulation (NIBS)** techniques have provided critical causal evidence linking activity within the dlPFC to cravings for and the consumption of hyperpalatable calorie-dense foods, substantially advancing our understanding of the association between dorsolateral lateral PFC input and consumptive behaviours. By using NIBS protocols, either **repetitive transcranial magnetic stimulation (rTMS)** or **transcranial direct current stimulation (tDCS)**, to induce temporary changes in cortical activity, prior work has demonstrated that increasing activity within the left and right dlPFC attenuates food cravings and the consumption of appetitive calorie-dense foods in individuals that report frequent and strong food cravings and/or have been diagnosed with

rTMS paradigms consist of a repetitive train of two or more pulses administered at a fixed frequency. Depending on the frequency of the stimulation, the effects of rTMS can be excitatory or inhibitory [77]. The resulting aftereffects typically last for up to 60 minutes poststimulation.

Transcranial direct current stimulation (tDCS): a NIBS technique in which saline-soaked electrodes of different polarities [anodal (excitatory) and cathodal (inhibitory)] are placed on different spots on the head; sometimes one electrode will be placed on the body and the other on the head. A small electrical current is passed between the electrodes, which changes neuron excitability by modifying the polarity shifts within the resting membrane potential. Although tDCS can result in similar after-effects and is easier to use than TMS methods, tDCS is less focal than TMS [77].

bulimia or binge eating disorder [26–28]. These findings are of importance, as they illustrate that increasing cortical activity within the PFC can modulate obesogenic eating behaviours in a theoretically meaningful way in persons susceptible to overconsumption under normal circumstances.

Recent work has also demonstrated that experimentally induced attenuation of cortical activity within the left dlPFC, via the use of inhibitory rTMS methods, can predispose individuals to the overconsumption of hyperpalatable calorie-dense foods, an effect that was directly mediated by stimulation-inductions reductions in inhibitory control [29,30]. What makes these findings so interesting is that, first, although participants reported stronger cravings for and directed more attentional resources towards rewarding high-calorie foods following active stimulation, when considered in parallel, the only reliable mediator of the consumptive effect were rTMS-induced changes in inhibitory control [30]. This suggests that eating behaviour itself is primarily modulated by inhibitory control abilities, a mediational pathway often assumed [3,5], but not previously tested. Second, in both studies, the participant sample consisted primarily of normal weight, healthy young adults, suggesting that attenuated activity within the dlPFC may precede obesogenic eating behaviours, and by extension weight gain, rather than obesity itself contributing to the impairments in dlPFC functionality; the latter is a fundamental aspect underlying the popular 'brain as an outcome' approach (discussed in the next section). Together, these findings build off the neuroimaging work described above by providing convincing causal evidence linking individual variations in PFC functionality to individual differences in dietary self-regulation. Although these mechanisms need to be explored further, these findings suggest that perturbations in PFC functionality may be a primary causal mechanism underlying individual vulnerability to overconsumption.

PFC Dysregulation as an Outcome of Obesity

In comparison to the brain as a predictor approach, the brain as an outcome approach postulates that any neurocognitive impairments are a direct outcome of obesity. Indeed, numerous cross-sectional studies have demonstrated that across the lifespan, persons with obesity perform more poorly on measures of global cognition, impulsivity, semantic and episodic memory, processing speed, and most notably, executive functioning [31–34]. This effect is comparable across executive function domains [33] and occurs independently of age, gender, and comorbid health conditions known to influence executive functioning, such as cerebrovascular disease, hypertension, and type 2 diabetes mellitus [33,35], suggesting that obesity itself results in the observed impairments in cognitive functioning.

Structural imaging studies have also consistently reported that in comparison with healthy weight individuals, otherwise healthy individuals with obesity have smaller whole brain volumes [36,37] and decreased regional grey matter volumes in several regions, including the hippocampus, anterior cingulate gyrus, dlPFC, orbitofrontal cortex (OFC), left temporal pole, vmPFC, frontopolar cortex, and cerebellum [38,39]. Additionally, obesity is associated with grey matter atrophy within the parietal, temporal, and frontal lobes, particularly the PFC. While frontal atrophy is observed in both younger and older adults, parietal and temporal lobe atrophy is more consistently observed in middle-aged and older adults [40]. Similarly, in children and adolescents with obesity, the observed reductions in grey matter volume are most pronounced in the frontal and limbic regions of the cortex [41]. However, the association between obesity and cortical thickness in children and adolescents is not equivocal within the literature, with prior work in large paediatric samples reporting null effects [42]. These obesity associated differences in brain morphometry are associated with obesity related impairments in executive functions [43], indicating that obesity related changes in grey matter morphometry may mediate

Box 3. Left Brain Versus Right Brain. Does it Matter?

With the increasing interest in the use of NIBS protocols in experimental and clinical settings as a treatment for both obesity [98] and eating disorders [99], hemispheric issues are becoming increasingly salient (i.e., should clinicians and researchers target the right or the left PFC). While there is evidence supporting a potential left–right dichotomy, it remains unclear whether it is the specific contribution of the right versus the left PFC that modulates obesogenic eating behaviours. Currently, there is evidence supporting both arguments.

The right brain hypothesis of obesity postulates that right PFC dysfunction may predispose an individual to obesity (see [100] for an overview). Evidence for this model is supported by the contention that damage to and hypoperfusion of the right PFC can increase nonhomeostatic eating behaviours [100], and that several aspects of cognitive control are dependent on right frontal activation, including inhibitory control and reward-based learning and decision-making [100]. Similarly, increased cortical thickness in the left PFC and decreased cortical thickness in the right PFC has been shown to correlate with genetic variance in BMI [101], which supports the contention that individual differences in the functional and structural integrity of the right PFC may modulate eating behaviours. As a result of the right brain hypothesis of obesity, many NIBS interventions and studies have targeted the right dlPFC [27,28].

Recently, increasing evidence has emerged to suggest that the left dlPFC also plays a crucial role in regulating dietary self-regulatory abilities. For instance, when individuals were asked to make decisions regarding which foods they would like to consume, increased activity in the left dlPFC was shown to be associated with healthier decisions [15] (i.e., individuals were more likely to select foods on the basis of health rather than taste). Likewise, cognitive control over calorie-dense food cravings has been shown to be dependent on the capacity of the left dlPFC to modulate activity in the ventral striatum [16], indicating that the left dlPFC plays a crucial role in regulating cravings for appetitive substances by modulating cortical activity within subcortical reward-regions. Several studies using inhibitory rTMS protocols have also demonstrated that experimental attenuation of the left dlPFC increases individual vulnerability to the overconsumption of appetitive calorie-dense foods via reductions in inhibitory control [29,30]. These findings are consistent with the notion that the left dlPFC is an important cortical region underlying both executive functioning and dietary self-regulation. Moreover, recent meta-analytic reviews have also demonstrated that the effect size for NIBS protocols in modulating executive functions [102], and consumptive behaviours and food cravings [26], is significantly higher in studies targeting the left relative to the right dlPFC. However, other reviews have not reported the same lateralisation effect in regards to food cravings and consumption [28,103], which can be attributed to methodological differences in data analyses and the scope of the review. Together, these data provide convincing evidence linking the left dlPFC to both executive functions and dietary self-regulation.

the relationship between obesity and cognitive functioning (i.e., the brain is acting as the primary meditator). In addition, reductions in white matter integrity in the form of demyelination or lesions in the white matter (white matter hyperintensities [44]) are observed in persons with obesity relative to healthy weight individuals. The proposed mechanisms underlying these obesity associated alternations in brain structure are outlined in Box 4.

Recently, several lines of work have demonstrated that behavioural and surgical weight-loss interventions can result in marked improvements in neurocognitive functioning and brain health

Box 4. Potential Mechanisms Underlying Obesity Associated Alternations in Brain Structure and Function

Obesity is associated with several cardiovascular and metabolic syndromes and diseases. It is the compounding negative effects of these conditions that are thought to explain the observed associations between peripheral adiposity and neurocognitive health. For instance, converging evidence has demonstrated that obesity associated insulin resistance also manifests as reductions in brain insulin sensitivity, and this can negatively impact both neurocognitive functioning and synaptic and structural plasticity within the hippocampus, dlPFC, and medial and temporal cortices [104,105]. Peripheral insulin resistance and hyperinsulinemia are both consequences of obesity that affect kidney function. The associated increase in sodium reabsorption ultimately results in hypertension or elevated blood pressure [106]. High arterial blood pressure promotes endothelial dysfunction and atherosclerosis, resulting in deficits in systematic and cerebral perfusion, which, in turn, exacerbates global and regional brain atrophy and white matter hyperintensities [107]. Alternatively, excess adipose tissue secretes a variety of inflammatory adipokines/cytokines, such as fibrinogen, interleukin (IL)-1β, IL-6, and C-reactive protein [108]. These inflammatory cytokines are able to cross the blood–brain barrier and stimulate the production and activation of central inflammatory mechanisms that prompt volumetric changes in global and regional grey matter and hippocampal neurodegeneration [109,110].

in persons with obesity. Significant improvements on measures on of executive functioning, memory, and attention are observed following voluntary weight loss [45] and bariatric surgery-induced weight loss [46] for up to 3 years postsurgery [47]. In children, significant increases in total brain and cerebellar grey matter volumes are observed following a 5 month behavioural weight loss program [48]. Functionally, bariatric-induced weight loss resulted in significant pre-to-post increases in dlPFC activation during a food appraisal task [49], and increased PFC cortical input coupled with reductions in striatal activation during a reward-based decision-making paradigm [50]. Together, these data demonstrate that weight loss can significantly improve neurocognitive functioning and brain health in persons with obesity, supporting the contention that obesity is causally associated with PFC dysfunction.

Reciprocal Relationship between PFC Dysregulation and Obesity

The available evidence reviewed above suggests that the brain can be both a predictor, causal agent, and outcome of obesity. Therefore, the question remains, are individual differences in the structure and function of the PFC a precursor to weight gain, or does excess **adiposity** lead to alterations in brain structure and function? Rather than a direct cause and effect, the relationship between the PFC and obesity is more likely to be reciprocal in nature (see Figure 1). That is, lower PFC input in response to food cues may increase individual susceptibility to the rewarding properties of calorie-dense foods, prompting overconsumption. Specifically, weaker cortical input and modulatory control over reward-regions of the cortex, coupled with reductions in cognitive control, reduces dietary self-regulatory abilities, increasing the likelihood that an individual will overconsume in the modern food-rich environment. Thus, over time, the repeated overindulgence in calorie-dense foods may evoke further functional dysregulation of the PFC and mesocorticolimbic dopaminergic system, exacerbating individual sensitivity to food rewards, promoting further overconsumption, subsequently leading to excessive adiposity. This excess adiposity, via the mechanisms described in Box 4, leads to the marked neurocognitive and neurophysiological impairments observed among persons with obesity. Consistent with this notion, the prolonged consumption of diets high in refined fats and sugars can lead to pronounced and enduring changes in PFC functionality and, subsequently, neurocognitive performance [51]. For instance, in humans, the acute and repeated administration of a hypercaloric high-fat diet results in subsequent impairments in attention, processing speed, memory, and global cognitive abilities [52–54].

These findings are further supported through diet manipulation studies with model organisms, including rats and mice, which allows not only meticulous control over diet parameters, but insight into the neurobiological outcomes of specific diets on cognitive function. These animal models are particularly important within the context of diet-evoked obesity, as manipulating diet in human participants for long-periods of time is complex and confounded by numerous factors, particularly adherence. Collectively, these studies have demonstrated that rodents fed either a high-sucrose, or a high-fat, high-sucrose diet show significant reductions in a major class of GABAergic interneurons, parvalbumin neurons, within the rodent homologue of the PFC [55,56] and hippocampus [55,57]. As these neurons are important for the regulation of behaviour and cognitive control, these findings highlight a potential mechanism via which calorie-dense diets may evoke functional impairments in cognitive control and dysregulation of the PFC. Likewise, the prolonged consumption of diets high in refined fats and sugars also stimulates the mesocorticolimbic dopamine system [58,59], evoking enduring changes in dopamine signalling within the mesocorticolimbic reward system and PFC as the terminal site of dopamine axons originating from the midbrain [51,60,61]. Considering that mesocortical dopaminergic inputs to the PFC are thought to play a pivotal role in regulating important aspects of executive functions, including inhibitory control [62,63], and that dopamine

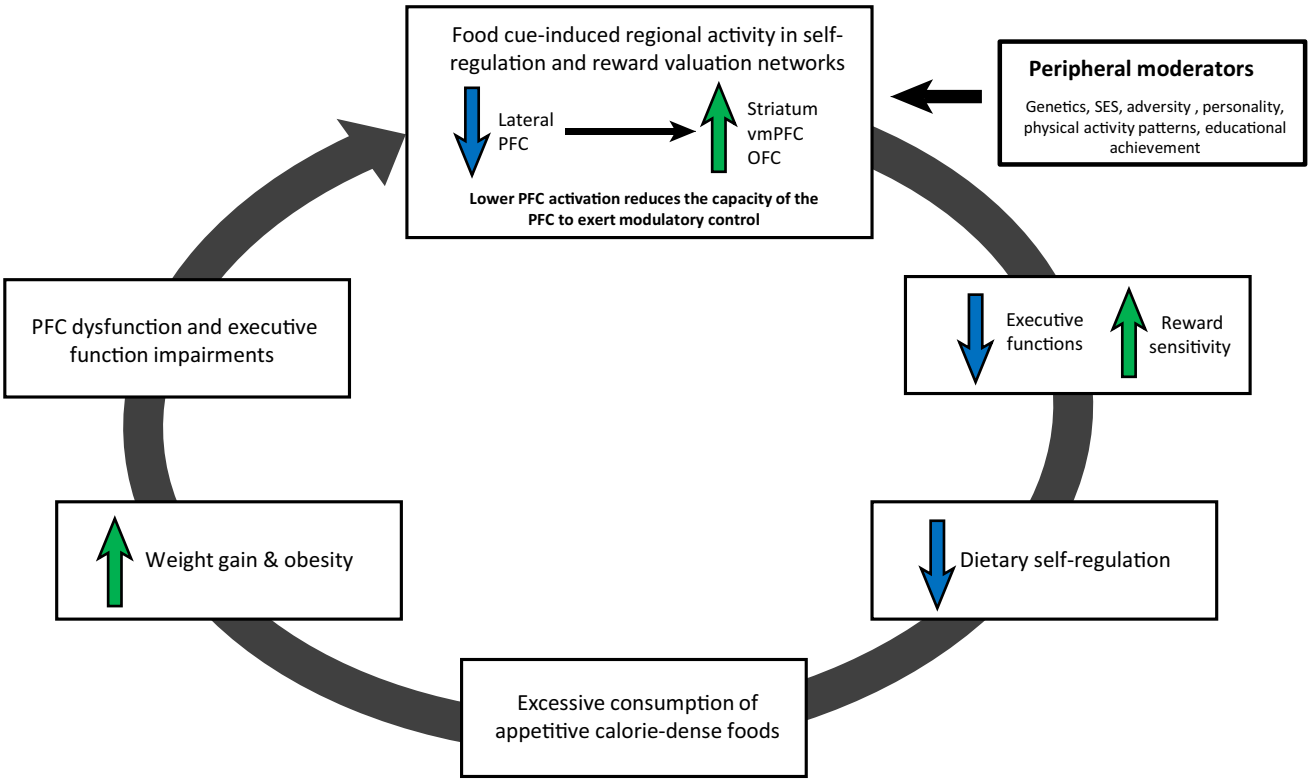

Figure 1. The Potential Reciprocal Relationship between the Prefrontal Cortex (PFC) and Diet-Evoked Obesity from Overconsumption of Hypercaloric Foods. Decreased activation in the lateral PFC in response to food cues reduces the capacity of the PFC to modulate reward valuation and processing in cortical and subcortical reward-regions, subsequently resulting in lower dietary self-regulation, increasing the likelihood of overconsumption of hyperpalatable calorie-dense foods. The persistent and sustained overconsumption of calorie-dense foods can lead to weight gain and, subsequently, obesity, which, in turn, results in the marked and enduring changes in mesocortical dopaminergic signalling, prefrontal functionality, and cognitive control. This, in turn, drives the maintenance of unhealthy eating behaviours. OFC, Orbitofrontal cortex; SES, socioeconomic status; vmPFC, ventromedial prefrontal cortex.

transmission in medial PFC regions is essential for the controlled coordination of actions and habits [64,65], these findings suggest that diet-induced changes in dopaminergic transmission within the PFC may play a key role in modulating the cognitive processes associated with dietary self-regulation. Together, the evidence from human and animal models suggests that both the prolonged and acute consumption of a calorie-dense diet may evoke functional dysregulation of the PFC, leading to further impairments in cognitive control, which, in turn, drives the persistent overconsumption of calorie-dense foods.

Such diet-evoked PFC dysregulation may be particularly profound when it occurs during critical neurodevelopmental periods, especially adolescence. Developmentally, adolescence is a sensitive period of marked neuroplasticity in which the brain undergoes considerable reorganisation and maturation, most notably within the PFC. The protracted developmental trajectory of the PFC in relation to the mesocorticolimbic dopamine system is thought to impede self-regulatory abilities, making adolescents more sensitive to immediate rewards, including palatable foods [66]; the development of subcortical reward-regions precedes the development of the cognitive control network. As such, the regulatory abilities that would typically enable individuals to override the temptations of calorie-dense foods are still

developing during adolescence, which may contribute to the poor dietary decisions typically observed within this population; adolescents consume more fast foods and refined sugars than any other age group [67,68].

Over time, such failures to regulate dietary decisions, either as a consequence of development immaturity and/or self-regulatory deficits, can disrupt the natural course of brain maturation and the development of the neurocircuitry underlying higher-order cognitive functions [69]. The excessive consumption of calorie-dense foods during this critical period is thought to chronically stimulate the still maturing mesocorticolimbic dopamine system, leading to pronounced and enduring neurobiological changes, including dysregulated PFC function and altered reward-processing (see [70] for a review). As such, it is hypothesised that obesogenic eating behaviours during this critical developmental period may derail normative neurodevelopmental trajectories with the PFC and mesocorticolimbic dopaminergic system, thereby exacerbating cognitive dysfunction, reward sensitivity, and the motivation to obtain rewards [70]. This, in turn, may promote overconsumption within the modern food-rich environment and establish maladaptive eating behaviours that drive the development of obesity [70].

Concluding Remarks

Together, the available evidence reviewed seems to suggest that individual differences in the structural and functional integrity of the PFC may play a crucial role in modulating individual level susceptibility to overconsumption in the modern environment, a notion that complements past work highlighting a similar reciprocal relationship between obesity and hippocampal dysfunction [71]. This reciprocal model directly addresses the shortcomings of current neurobehavioural models of obesity by highlighting that vulnerability to obesogenic eating behaviours may be related to individual differences in PFC control over cortical and subcortical reward-region responsivity to food cues.

Specifically, it is these differences in the capacity of the PFC to modulate the reward-regions of the cortex that drives the persistent consumption of calorie-dense foods, rather than reward-region responsivity itself. The cognitive control mechanisms implemented by the PFC enable the dietary self-regulatory abilities that are necessary to exert conscious control over food choices and consumptive behaviours. Weaker modulatory control predisposes individuals to the overconsumption of hyperpalatable energy-dense foods. Then, over time, the prolonged consumption of calorie-dense foods may lead to the marked and enduring changes in mesocortical dopaminergic signalling and PFC functionality, typically observed in persons with obesity.

While the available evidence seems to suggest the potential for a reciprocal relationship, most of the available evidence supporting this hypothesis is strongly dependent on cross-sectional work or animal models, limiting the ability to draw causal conclusions regarding the nature and directionality of the effect. As such, even though this notion is grounded in theory, the successful development of this model will demand progression beyond simple cross-sectional data and animal work. Specifically, there is a need for prospective longitudinal work, especially in children and adolescent populations. Mapping the development of dietary self-regulation to the development of the PFC may provide important insight into mechanisms underlying PFC modulation of dietary self-regulatory abilities and the factors that can influence the development of such abilities (see Outstanding Questions). Further, there are several potential moderators of this effect (Box 5) and therefore it cannot be concluded whether the effect is driven by the moderator's effect on the brain or whether PFC activity is a true causal agent underlying individual differences in dietary self-regulation. Finally, while the incorporation of a PFC model of obesity vulnerability can be used to explain individual differences in dietary self-regulation, it

Outstanding Questions

Does dietary self-regulation develop in a similar manner as cognitive control (i.e., in conjunction with the maturation of PFC)? If so, can we use developmental neural trajectories to understand why some individuals are more proficient at exerting dietary self-regulation than others?

How do dietary self-regulatory abilities change over the course of the lifespan? As we age, do we become more susceptible to the temptations of appetitive calorie-dense foods due to age-related declines in executive functions and brain structure and function? Prospective longitudinal work, especially during critical developmental periods, is essential to fully elucidate whether individual differences in the structural and functional integrity of the PFC precedes weight gain and obesity, or is a neuroadaptation caused by excessive adiposity.

What lifestyle interventions are the most effective at optimising the structural and functional integrity of the PFC, and can such intervention-induced changes in brain health foster improved dietary self-regulation? For instance, the beneficial effects of aerobic exercise and resistance training on brain health and executive functions are well documented [73,74]. Randomized trials have consistently reported that exercise interventions can induce positive changes in regional grey matter volumes with the PFC and hippocampus and increase white matter tract integrity. Therefore, it is plausible that exercise interventions may also improve dietary self-regulation via exercise-induced improvements in brain health.

Box 5. Potential Moderators of the Relationship between the PFC Functionality, Cognitive Control, and Obesity

Several distal and contextual influences may moderate the association between PFC activity as a predictor and/or outcome of obesity. These may include:

- Socioeconomic status (SES) has been shown to be a strong predictor of executive functions and brain development [111]. Individuals that grew up in lower SES households typically perform more poorly on executive function and language measures, and show marked impairments in structure and function of the lateral PFC [111].
- Early life adversity, including that which falls within normative ranges [112], can profoundly impact developmental neural trajectories, especially within the mesocortical dopaminergic system. Specifically, exposure to maltreatment or adversity during childhood impacts the functional calibration of the brain's reward system, resulting in increased striatal dopamine release in response to rewarding stimuli [113]. This manifests as elevated impulsivity/heightened sensitivity to immediate rewards and impairments in reward-based decision-making and learning [113]. Recent evidence has also linked childhood adversity to structural alternations in later developing cortical regions, specifically the PFC and hippocampus [114,115]. Such alterations could manifest as impairments in executive functioning or cognitive control, which, in turn, may modulate dietary self-regulatory abilities.
- Obesity related differences in cortical thickness, regional brain volumes, and performance on cognitive tasks have been attributed to shared genetic factors [101], indicating that genetic differences may play a role in modulating individual differences in PFC-mediated dietary self-regulation.
- Personality traits have been shown to explain a small percentage of the individual variance in BMI (2.3%). Specifically, increased neuroticism and decreased conscientiousness was associated with higher BMIs [116], and studies suggest that a significant proportion of the variability in obesogenic behaviours may be attributable to overlap between personality traits and executive function [117]
- Physical activity patterns have been shown to be associated with executive functions and the structural and functional integrity of the brain. Habitual engagement in more physically active behaviours is positively associated with performance on executive function measures and scholastic aptitude [118,119]. In addition, cardiorespiratory fitness is associated with white matter tract integrity and cerebral blood flow to the hippocampus [120,121]. Causal evidence from randomized interventions have consistently demonstrated that both aerobic exercise and resistance training can improve executive functions and the structural and functional integrity of the underlying cortical regions [73,74]. While more evidence is necessary to assess whether physical activity patterns influence dietary self-regulatory abilities and consumptive patterns, the observed association between physical activity and executive functions suggests the possibility.
- Educational achievement has been shown to explain some of the genetic variance in BMI and cognitive abilities [122,123]. Higher education levels have been shown to be associated with lower BMIs after accounting for shared and nonshared environmental influences [123] and higher IQ scores [122].

cannot account for large-scale societal differences that may influence dietary choices, including food availability, access to healthy food items, and resources to purchase healthier food items. However, it is possible that variations in PFC functionality may interact with these large-scale societal factors to influence consumptive habits.

Nonetheless, the incorporation of specific patterns of PFC responsivity and cognitive control into existing neurobehavioural models of obesity would enable researchers to develop a more convincing neurobiological phenotype of obesity. Moreover, this will define a more comprehensive model of why some individuals are more adept at regulating appetitive calorie-dense food consumption than others, which, in turn, can be leveraged to develop novel and more effective interventions that would both enable researchers and clinicians to identify those individuals that may be more likely to respond to a given intervention, and inform strategic prevention interventions aimed at mitigating obesity onset. For instance, instructing individuals to focus on the healthiness of food items, rather than the taste, has been shown to be effective in reducing taste value signals within vmPFC, an effect that was modulated by increased activity in the dlPFC [72]. This suggests that integration of such messages into media advertisements or product packaging, similar to tobacco warnings, may potentiate dietary self-regulatory abilities, enabling individuals to make healthier dietary choices. Further, significant improvements in executive functions, grey matter morphometry, and white matter tract integrity are observed following randomized aerobic exercise and resistance training interventions [73–75].

These effects are most pronounced within the PFC and hippocampus, key cortical regions implicated in the development and maintenance of obesity, highlighting the potential of such interventions in mitigating obesity risk. Considering the association between obesity and obesogenic eating behaviours and PFC dysregulation, and that the PFC follows a protracted development, the timing of preventative interventions may be especially pertinent. Targeted interventions in children and adolescents, such as school-based exercise interventions, may potentially prevent the viscous cycle of obesity.

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