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Review

Neuroimaging and neuroendocrine insights into food cravings and appetite interventions in obesity

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Abstract

This article reviews the previous studies on the distinction between food cravings and appetite, and how they are regulated by hormones and reflected in brain activity. Based on existing research, food cravings are defined as individual preferences influenced by hormones and psychological factors, which differ from appetite, as they are not necessarily related to hunger or nutritional needs. The article also evaluates the neuroimaging findings about food cravings, and interventions to reduce food cravings, such as mindfulness training, alternative sweeteners, non-invasive brain stimulation techniques, cognitive-behavioral therapy, and imaginal retraining, and points out their advantages, disadvantages, and limitations. Furthermore, the article delves into the potential future directions in the field, emphasizing the need for a neuroendocrine perspective, considerations for associated psychiatric disorders, innovative clinical interventions, and emerging therapeutic frontiers in obesity management. The article outlines the neuro-endocrine basis of food cravings, including ghrelin, leptin, melanocortin, oxytocin, glucagon-like peptide-1, baclofen, and other hormones and their brain regions of action. The article argues that food cravings are an important target for obesity, and more research is needed to explore their complex characteristics and mechanisms, and how to effectively interact with their neuro-endocrine pathways. The article provides a new perspective and approach to the prevention and treatment of obesity.

Keywords: food cravings; fMRI; appetite; obesity; neuro-endocrine

Introduction

Obesity has rapidly become a global epidemic, with food cravings standing out as a significant contributor and a key psychopathological dimension of this health concern. As a prevailing psychological phenomenon, food cravings are commonly characterized by intense desires or urges to consume specific types of food, exerting a notable influence on individuals' food choices and behaviors (Kozlowski & Wilkinson, 1987; Weingarten & Elston, 1990). It is noteworthy that the intensity of food cravings may vary among individuals, with certain individuals experiencing more pronounced manifestations (O'Brien *et al.*, 1998). Dysregulated food cravings can contribute to detrimental eating patterns, including binge eating, emotional eating, and disordered eating behaviors (Milos *et al.*, 2017). Furthermore, there is mounting evidence linking food cravings to the onset and progression of obesity and related metabolic disorders, with research suggesting a bi-directional relationship between food cravings and weight gain (Booth *et al.*, 2018). On the one hand, if food cravings develop into food addiction, binge eating disorder or obesity, or significantly interfere with daily life, it is necessary to take measures for intervention and treatment (Boswell & Kober, 2016). Given the significant variations in the intensity and nature of food cravings among individuals, it is crucial to recognize and address more pronounced manifestations.

Addressing these food cravings has led to the exploration and trial of a multitude of interventions, such as mindfulness interventions, alternative sweeteners, non-invasive brain stimulation techniques, cognitive-behavioral therapy, and imaginal retraining. Mindfulness interventions aim to shift the focus from the goal of weight loss to the process of eating. (i) By practicing mindful eating, such as eating slowly and paying attention to bodily sensations, participants may not only indirectly reduce their daily calorie intake, but also consume less food driven by cravings and stress (Schnepper *et al.*, 2019). Several previous studies have indicated that regular or excessive craving for refined sugar can lead to being overweight, obesity, diabetes, and metabolic syndrome (Chan *et al.*, 2014). Additionally, alternative natural sweeteners such as honey, fructose, high fructose corn syrup, and maple syrup have been found to have similar undesired metabolic effects (Johnson *et al.*, 2013; Wölnerhanssen *et al.*, 2020). (ii) In the treatment of severe and enduring anorexia nervosa and morbid obesity, invasive brain stimulation techniques have shown promising results (Jauch-Chara *et al.*, 2014). Some researchers have also employed transcranial direct current stimulation targeted at the dorsolateral prefrontal cortex (DLPFC), in conjunction with psychological education, dietary modification, and physical activity, to potentially ameliorate food cravings (Beaumont *et al.*, 2022; Kekic *et al.*, 2014). However, the efficacy of these interventions is limited, and excessive and inappropriate use of sweeteners can contribute to obesity by contrast (Hootman *et al.*, 2017). (iii) Cognitive-behavioral therapy can reduce cravings but does not

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lower BMI (body mass index) (Stapleton *et al.*, 2016). The newly researched approach of imaginal retraining remains unknown as to its long-term efficacy (Wirtz *et al.*, 2021). However, the overall efficacy of these interventions remains inconsistent, with numerous approaches failing to yield positive outcomes, further highlighting the challenge of managing food cravings.

The inconsistent results arising from various interventions underscore the need for a closer examination of the methodologies used to understand and measure food cravings. A primary challenge in this realm is the absence of universally accepted definitions and standard measurement tools for food cravings, which can sow confusion and potentially conflate with concepts such as appetite, food reward craving, and emotional eating. Several tools exist to measure food cravings, each with its unique merits and limitations. (i) Self-report questionnaires, such as the Craving Experience Questionnaire (Andrade *et al.*, 2012), Strength version Food Cravings Questionnaire-State (Cepeda-Benito *et al.*, 2000), and Food Cravings Inventory (White *et al.*, 2002), are the most popular given their ease of administration (Taylor, 2019). On the other hand, the Ecological Momentary Assessment offers real-time data collection through devices such as smartphones, providing valuable insights into the temporal patterns and contexts of food cravings (Shiffman *et al.*, 2008). (ii) Behavioral tasks, such as the food choice task or the food Stroop task, can assess the impact of food cravings on decision-making and cognitive processes (Liu *et al.*, 2022). (iii) Most significantly, neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), can provide information about the neural mechanisms underlying food cravings (Pelchat *et al.*, 2004). In neuroimaging studies, food cues are widely used materials. visual food cues, such as pictures and videos, are highly effective in eliciting food cravings and related bodily responses (Jansen *et al.*, 2003). Conditional cues, such as visual food cues, can evoke various physiological reactions, including increased salivation (Nirenberg & Miller, 1982), increased heart rate (Nederkoorn & Jansen, 2002), increased stomach activity (Nederkoorn *et al.*, 2000), and increased neural activity in the ventromedial striatum (Tang *et al.*, 2012). Most importantly, the effects of visual food cues on food cravings are more robust than those of olfactory cues (Boswell & Kober, 2016). The recent study by Koban, Wager, and Kober introduces an fMRI neuromarker for drug and food cravings visual stimuli (Koban *et al.*, 2023). Despite the diversity of these tools, they all grapple with limitations impacting their reliability and validity.

Given the current fragmented understanding and the mixed results from interventions, it is imperative to re-evaluate food cravings. Instead of viewing them merely as psychological impulses, we should consider them as intricate processes intertwined with the neuroendocrine system. While current methodologies, such as questionnaires and behavioral tasks, provide insights into behaviors such as delay discounting, they fall short in uncovering the deeper roots of these cravings (Fazzino *et al.*, 2022). This brings our attention to the endocrine system, a potentially pivotal player in influencing food cravings through its impact on the brain. Future research, we believe, should pivot toward interventions targeting the endocrine system, exploring the neuroendocrine axis, food composition, dosage, and metabolic processes. Such directions promise a holistic understanding of obesity interventions. It is paramount to define and measure food cravings accurately, especially given their time-sensitive and multifaceted nature. By embracing this nuanced perspective, we might pave the way for more efficacious interventions, unraveling the intricate relationship between cravings, obesity, and the neuroendocrine system.

Methods

Selection strategy

We employed a comprehensive bibliometric analysis of articles sourced from the Web of Science database and PubMed, spanning from January 1968 to September 2023. Our methodology aligned with the PRISMA guidelines (Moher *et al.* 2009), providing a structured approach to literature search and article selection. We centered our searches on the convergence of two primary themes: food craving* and endocrin*. Articles from non-relevant journals and those categorized under Institute for Scientific Information (ISI) such as Neurosciences, Psychiatry, Clinical Neurology, Substance Abuse, Pharmacology Pharmacy, Behavioral Sciences, Psychology-Clinical, Medicine General Internal, Psychology, Biochemistry Molecular Biology, and Multidisciplinary Sciences were excluded. We had pre-registered this study, with all the data being accessible at https://osf.io/uzjw6.

Selection criteria

Once irrelevant articles were filtered out, two of our researchers (H.Z. and J.H.) collaboratively confirmed the selected collection and then refined the dataset for a more focused bibliometric evaluation. In instances of discrepancies, H.Z. and J.H. deliberated to reach a unanimous decision. In rare cases where consensus remained elusive, a third member (C.W.) mediated the decision-making process.

Included in our systematic reviews were:

(i) a diverse range of document types such as original articles, review articles, editorials, opinions, and proceedings articles;
(ii) articles exclusively penned in English;
(iii) articles falling under specific relevant ISI categories;
(iv) studies addressing various facets of food craving intertwined with endocrine;
(v) articles in which at least one of the stated MeSH terms appeared within their abstracts.

Perspective

Measurement should take into account multiple dimensions

Food cravings are defined as a strong motivation to eat that is induced by hedonic eating and triggered by external stimuli such as visual or olfactory food cues (Harvey *et al.*, 2005). In the obese population, food cravings can account for 11% of the variation in body weight (Boswell & Kober, 2016). In obese individuals and patients with eating disorders, food-related attention biases are more pronounced, which may lead to excessive focus on and craving for food (Hendrikse *et al.*, 2015; Werthmann *et al.*, 2015). Mild cravings may trigger pleasure eating, similar to how food consumption increases among spectators during a football game victory (Chang, 2021). Chronic cravings increase the risk of developing diseases, and severe cravings can lead to binge eating and long-term weight gain (Chao *et al.*, 2015). However, food cravings are complex and multidimensional constructs that involve various aspects, such as individuality, time, and gender.

Neurological insights into food cravings

Recent decades have witnessed remarkable advancements in functional neuroimaging techniques, which have significantly propelled the field of diet and obesity within cognitive neuroscience forward. These advancements have primarily centered on

observing changes in brain dynamics, be it hemodynamics or electrophysiology, during exposure to food-related stimuli, aiming to decode the neural basis of hedonic and reactive responses (Leng *et al.*, 2017). In comparison to lean individuals, both lean individuals and individuals with obesity exhibit activations in brain regions associated with food intake and food cues, which include areas such as the orbitofrontal cortex, insula, amygdala, hippocampus, hypothalamus, and prefrontal cortex, as well as the anterior cingulate cortex (Carnell *et al.*, 2012; Devoto *et al.*, 2018). In an experiment with 34 healthy, non-obese participants, the influence of insulin infusion on the brain's response to visual cues of high- and low-calorie foods was investigated using fMRI. Results indicated that while visual food cues elicited strong brain responses in motivational/reward and cognitive control areas, these responses were not attenuated by hyperinsulinemia, suggesting that the overpowering external food signals in our environment might override internal homeostatic hormonal signaling, contributing to the current obesity epidemic (Belfort-DeAguiar *et al.*, 2016).

A series of studies have particularly underscored the reactive patterns of the brain during food cravings. For instance, research has found that food craving tasks activate specific regions like the striatum and insula. An illustrative study observed that after an overnight fast, obese females exhibited heightened activation in reward/motivation centers such as the nucleus accumbens (NAc)/ventral striatum when exposed to high-calorie food images, like cheesecake (Stoeckel *et al.*, 2008). Echoing these findings, another study with adolescents demonstrated that overweight participants had amplified brain activation in areas such as the frontal lobe and insula during a food choice task involving appetizing food cues (Moreno-Padilla *et al.*, 2018). The neural responses to these food cues are not confined to MRI techniques. EEG-based studies have linked food cravings with late positive potential. In one such study, both healthy controls and individuals with binge eating disorder displayed elevated late positive potential amplitudes in response to chocolate visuals, suggesting the power of visual food stimuli in eliciting cravings (Wolz *et al.*, 2017).

Further diving into the neurophysiological realm, positron emission tomography scans have associated food cravings with metabolic alterations. A noteworthy study juxtaposed brain glucose metabolism between obese and non-obese males under varied food stimulus conditions. Results highlighted that food stimuli invariably increased glucose metabolism in regions such as the prefrontal cortex. Moreover, obese males showed distinctive metabolic patterns in certain regions such as the pregenual anterior cingulate cortex during inhibitory food stimuli exposure (Wang *et al.*, 2020).

The dynamics of smoking habits coupled with food cravings have also been explored. A study contrasting the neural responses of smokers and non-smokers on exposure to favorite food cues indicated a subdued activation in motivation and reward regions among smokers, potentially elucidating their relatively lower BMI (Jastreboff *et al.*, 2015). In another nuanced observation, obese participants showed pronounced neural activity in regions such as the cortico-limbic-striatal circuit when exposed to favorite foods and stress cues. This surge in brain activity was found to have direct correlations with appetite and insulin levels, marking the intricate ties between neurophysiological processes and hormonal fluctuations (Jastreboff *et al.*, 2013). In conclusion, the richness of these findings underscores the potential of modern neuroimaging in unearthing the intricacies of food cravings and their ties to obesity. The mosaic of observed neural patterns and their interplay with various physiological factors pave the way for a more nuanced understanding of diet, cravings, and metabolic health.

Distinguishing food cravings from appetite

Food cravings and appetite, although both related to food intake, exhibit distinct characteristics, targets, and underlying mechanisms (Fig. 1). Specifically, while food cravings are object-specific, often triggered by visual cues or social contexts (Fig. 1a), appetite is more influenced by physiological states such as hunger and satiety (Fig. 1b). This distinction becomes evident when noting that individuals may have an intensified desire for carbohydrate-rich foods during low blood sugar episodes, even when not necessarily hungry (Strachan *et al.*, 2004).

Notably, food cravings do not necessarily align with fasting times and do not always correlate with appetite (Fig. 1c). They become a concern when leading to overconsumption or binge-eating behaviors (Challet, 2019). On the other hand, while cravings target specific food items, appetite manifests as a general feeling of hunger without pinpointing any particular food object (Pelchat, 2002). Appetite itself can be influenced by physiological changes such as exercise intensity, daily rhythms, and fatigue levels. For example, a study involving 30 sedentary adults compared the effects of two different exercise regimens on mood, energy, and cognitive function. Interestingly, short, regular treadmill sessions throughout the day not only boosted energy but also affected appetite and mood positively, suggesting exercise patterns might impact appetite regulation (Bergouignan *et al.*, 2016)

In another study examining the effects of chronic glucocorticoid exposure on appetite and cravings, findings indicated a more pronounced influence on cravings than on hunger, further emphasizing the distinct nature of the two (Geer *et al.*, 2016). Additionally, while both cravings and appetite can be satiated by consuming food, they seem to have different underlying mechanisms. Our observations point to some overlap in the biological clock's influence over both (Fig. 1d), yet specific triggers such as visual cues tend to exert a stronger pull on food cravings than on general appetite (Schumacher *et al.*, 2019), In conclusion, it is imperative to distinguish between food cravings and appetite in research, as both, while interconnected, are distinct phenomena with unique characteristics and triggers.

Temporal and physiological dimensions of food cravings

Food cravings and appetite, while intertwined, are influenced by distinct physiological and temporal factors. Hormonal fluctuations, for instance, play a significant role in modulating these cravings, especially in women.

During various menstrual cycle stages, such as ovulation and the luteal phase, women report intensified food cravings and appetite, particularly for certain food types (McVay *et al.*, 2012). Hormonal dynamics further interplay with dietary desires; for instance, the estradiol–leptin axis might be influencing food intake and cravings during the menstrual cycle (Krishnan *et al.*, 2016). Additionally, the impact of hyperandrogenism in overweight women suggests a need to explore the relationship between elevated androgen levels and food cravings (Lim *et al.*, 2009).

Pregnancy also introduces unique craving dynamics. While a sizable portion of pregnant women report food cravings, these do not always influence overall dietary intake or maternal glucose levels (Hill *et al.*, 2016). Intriguingly, cravings for sweet foods during pregnancy have been linked with the onset of gestational diabetes mellitus (Belzer *et al.*, 2010).

Outside the realm of hormonal factors, other physiological cues also influence food cravings. For example, an inadequate protein intake can instigate compensatory changes in cravings (Griffioen-

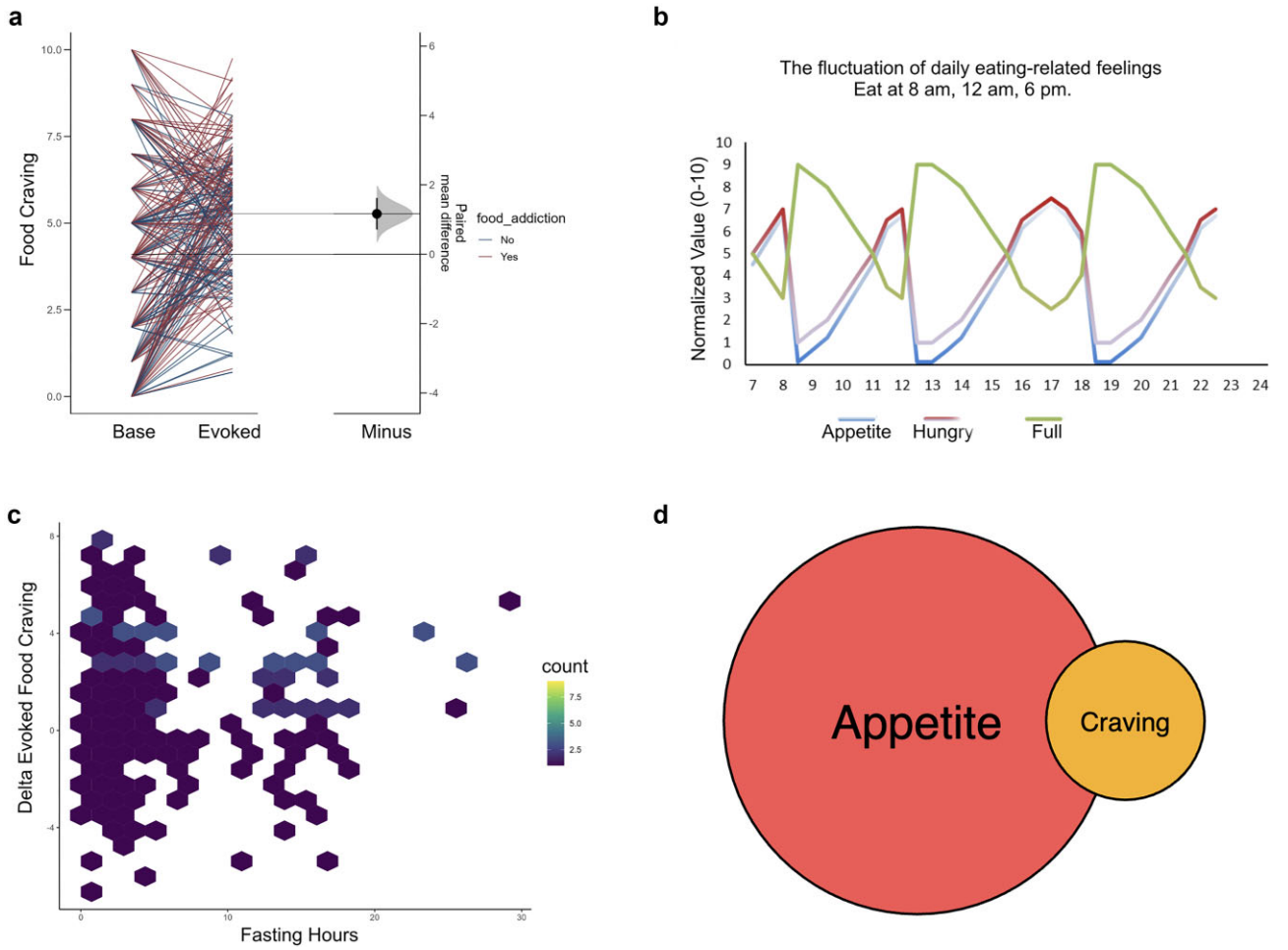

Figure 1: The available evidence supports that food cravings are distinct from appetite. (**a**) Food cravings can be induced by food pictures, regardless of whether the respondent has a lapsed addiction ($n = 213$). (**b**) Appetite, hunger, and satiety are directly related to eating behavior and also to fasting. (**c**) Changes in food cravings are independent of the duration of fasting. (**d**) Manifestations of food cravings may overlap with appetite, but can be distinguished by the eating state.

Roose *et al.*, 2012). Daily cycles, such as those influenced by breakfast consumption, can modulate feelings of fullness and satiety (Chowdhury *et al.*, 2015). Furthermore, consuming whole-grain rye porridge for breakfast compared to refined wheat bread extends the feeling of fullness up to 8 hours after breakfast (Isaksson *et al.*, 2008). Interestingly, these cycles may further be influenced by factors such as light exposure or even air pressure (Challet, 2019). In a study involving 87 adolescents, food cravings were found to be associated with the severity of loss-of-control eating in both genders. Moreover, in naturalistic settings, the association was modulated by reproductive hormones (estradiol and progesterone) in females but not in males, highlighting the gender-specific interplay between hormonal fluctuations and eating behaviors during adolescence (Parker *et al.*, 2021). In contrast appetite is more affected by hormones.

Certain conditions such as PCOS or Cushing's Syndrome introduce their own craving dynamics. For example, women with PCOS demonstrate a relation between metabolic factors and food cravings (Stefanaki *et al.*, 2023). Another study involving obese ($n = 340$), overweight ($n = 70$), and weight-normal ($n = 45$) women with PCOS, along with weight-normal healthy women ($n = 40$), analyzed the prevalence of binge eating behaviors and food cravings using various questionnaires. Notably, 60% of obese women with PCOS were categorized with binge eating behaviors, and multivariate regression revealed factors including total food cravings, emotional eating scores, and BMI as significant predictors of binge-eating symptom scores in PCOS patients (Jeanes *et al.*, 2017). Whereas in Cushing's Syndrome, abnormal glucocorticoid levels might be driving changed food-reward responses (Moeller *et al.*, 2016). The research compared the appetite symptoms of type 2 diabetes mellitus (T2DM) patients with non-diabetic controls. Results revealed higher carbohydrate cravings in patients with T2DM, especially those with uncontrolled blood sugar, underscoring a potential link between carbohydrate cravings and blood glucose management (Yu *et al.*, 2013).

In conclusion, while both food cravings and appetite play pivotal roles in dietary habits, it is clear they are influenced by a myriad of physiological and temporal factors. Further research might offer more nuanced insights into their complex interplay.

The factors influences on food cravings

Regarding genetic and physiological elements, food cravings are also individualized by food preference, and at the genetic level, functional mutations of the TAS2R38 gene are associated with higher consumption of bitter vegetables and fruits and lower consumption of beverages (Choi, 2019). Moreover, these mutations have been found to increase the intake of sweet foods in children aged 1–6 years (Pawellek *et al.*, 2016). Individuals with heightened

sensitivity to salty and sweet flavors are more likely to consume high-calorie foods during periods of poor sleep quality (Kracht *et al.*, 2019), whereas their intake of high-calorie foods is reduced when they experience better sleep quality (Lv *et al.*, 2018).

Regarding socio-cultural factors, our environment, both immediate and broader, can shape our food desires. Family dynamics and role modeling can affect dietary preferences, encouraging healthier habits like increased physical activity and fruit and vegetable consumption (Pearson *et al.*, 2009). Moreover, distinct preferences emerge in different demographics; for instance, college males typically gravitate toward energy drinks, while females favor juices (Deliens *et al.*, 2015).

Psychological states and mental mealth influence cravings. Our mental well-being has a profound effect on them. Psychological and behavioral factors can predict the success or failure of weight loss endeavors, with cravings for high-fat foods often leading to greater weight loss, while carbohydrate cravings can predict weight gain (Liu *et al.*, 2020). Moreover, certain mental health conditions, such as early-stage psychosis and bipolar disorder, display unique food craving patterns. Elevated leptin levels in psychosis patients (Martorell *et al.*, 2019) and ghrelin-associated cravings in patients with bipolar disorder emphasize the intricate relationship between mental health and dietary desires (Platzer *et al.*, 2020). Additionally, conditions such as binge eating disorder show a strong link between psychological stress and food cravings (Rosenberg *et al.*, 2013).

Sometimes, our eating habits are influenced by significant external events. For instance, the COVID-19 pandemic lockdown had a profound effect on dietary patterns, especially among patients with T2DM, with observed shifts in vegetable, sugar, and snack consumption (Ruiz-Roso *et al.*, 2020).

Neuroendocrine interventions are the focus of food craving control

Many studies have neglected to differentiate the neural circuits of hunger and food cravings, and have assumed that postprandial food cravings are the same as hunger. Although some circuits, such as elevated agouti-related peptide (AgRP) neural activity, can drive feeding in both fed and hungry states (Wang *et al.*, 2021), the role of reward and motivation in food cravings have been poorly explored, possibly due to the difficulties in measuring food cravings in animal models. Interventions for appetite and cravings require a comprehensive approach that involves policies, guidance, and cognitive interventions. A naturalistic longitudinal 6-month follow-up study revealed that cortisol and appetite-related hormones, such as ghrelin and leptin, moderated the relationship between stress and changes in food cravings and weight (Chao *et al.*, 2017). A deeper comprehension of the neuroendocrine mechanisms underlying appetite and cravings will enable more precise, systematic, and specific interventions. The new pathway of the craving of obesity treatment on metabolic approach is depicted in Fig. 2. The following sections will talk about the role of leptin, ghrelin, oxytocin, melanocortin, GLP-1, baclofen, and bariatric surgery in regulating food cravings and their potentials for intervention, as well as the challenges and limitations of leptin treatment.

Leptin

Leptin is a hormone produced in adipose tissue that primarily functions to maintain energy homeostasis by regulating food intake and energy expenditure (Considine *et al.*, 1996). In individuals with congenital leptin deficiency, acute exogenous administration of leptin can significantly reduce activation of the NAc and caudate nucleus in response to visual food stimuli, thereby reducing the brain's perception of food (Farooqi *et al.*, 2007). Weight loss leads to an enhanced response to high-calorie foods, which is also caused by a decrease in leptin levels (Bodell & Keel, 2015; Keel *et al.*, 2017). These findings suggest that leptin may play a mediating role in the relationship between weight suppression and the maintenance of bulimic symptoms. The main neuroendocrine pathway that may be responsible for this effect involves leptin acting in the arcuate nucleus of the hypothalamus, activating pro-opiomelanocortin (POMC)-containing neurons that produce anorexigenic molecules such as α-melanocyte stimulating hormone, and inhibiting orexigenic neuropeptide Y (NPY) and AgRP-containing neurons. Consequently, under conditions of low energy reserves, such as low body fat levels or fasting, leptin levels decrease, leading to reduced activity of POMC neurons and increased activity of NPY and AgRP neurons, ultimately resulting in increased appetite, food cravings, and food intake (Cone, 2005; Huszar *et al.*, 1997). An experimental study on the visual stimuli of high-calorie foods in obese adolescents also demonstrated that higher levels of endogenous leptin were associated with increased neural activation in response to high-calorie food images ($P < 0.05$). Compared to lean individuals, obese individuals showed significantly higher neural responses in various regions (including striatal, limbic, and cortical regions) when presented with images of high-calorie foods versus non-foods, with effect sizes ranging from 0.49 to 0.59 (Jastreboff *et al.*, 2014). Unfortunately, in studies of metreleptin signaling pathways in human adipose tissue and peripheral blood mononuclear cells, saturation is reached at ~50 ng/ml (Moon *et al.*, 2015). Furthermore, clinical trials have found that leptin treatment has no significant impact on the body weight of obese patients (Moon *et al.*, 2011). The hope of controlling obesity through reduced appetite and food cravings with leptin has become a luxury. However, recent progress has shown that short-term leptin administration can alter food intake during the refeeding period after fasting, and long-term leptin treatment can reduce fat mass and body weight. It is also acknowledged that leptin does not affect energy expenditure and that baseline leptin levels cannot predict the magnitude of weight loss (Chrysafi *et al.*, 2020; Perakakis *et al.*, 2021). Moreover, leptin is not a thermogenic hormone, and its weight loss effects do not intensify due to increased thermogenesis (Fischer *et al.*, 2020). Therefore, more research is needed to demonstrate its potential for intervening in food cravings.

Ghrelin

Ghrelin and leptin have opposing roles in the regulation of energy intake and expenditure. Ghrelin, which is a 28-amino acid peptide primarily synthesized in the gastric mucosa, acts as an endogenous ligand for the growth hormone secretagogue receptor type 1a (GHS-R1a). It has been found to increase neural responses associated with food cravings. In studies involving healthy individuals, the injection of ghrelin has been shown to enhance activation in the pallidum and insula in response to food-related cues. This peptide plays a crucial role in stimulating growth hormone secretion while concurrently promoting appetite, thereby contributing to an overall increase in body weight (Tschöp *et al.*, 2000). Ghrelin has been found to promote olfactory cues by adjusting odorant detection thresholds of olfactory neurons in the olfactory bulb (Tong *et al.*, 2011), while also stimulating increased activity of NPY/AgRP neurons in the hypothalamus and suppressing POMC-expressing neurons in the hypothalamic arcuate

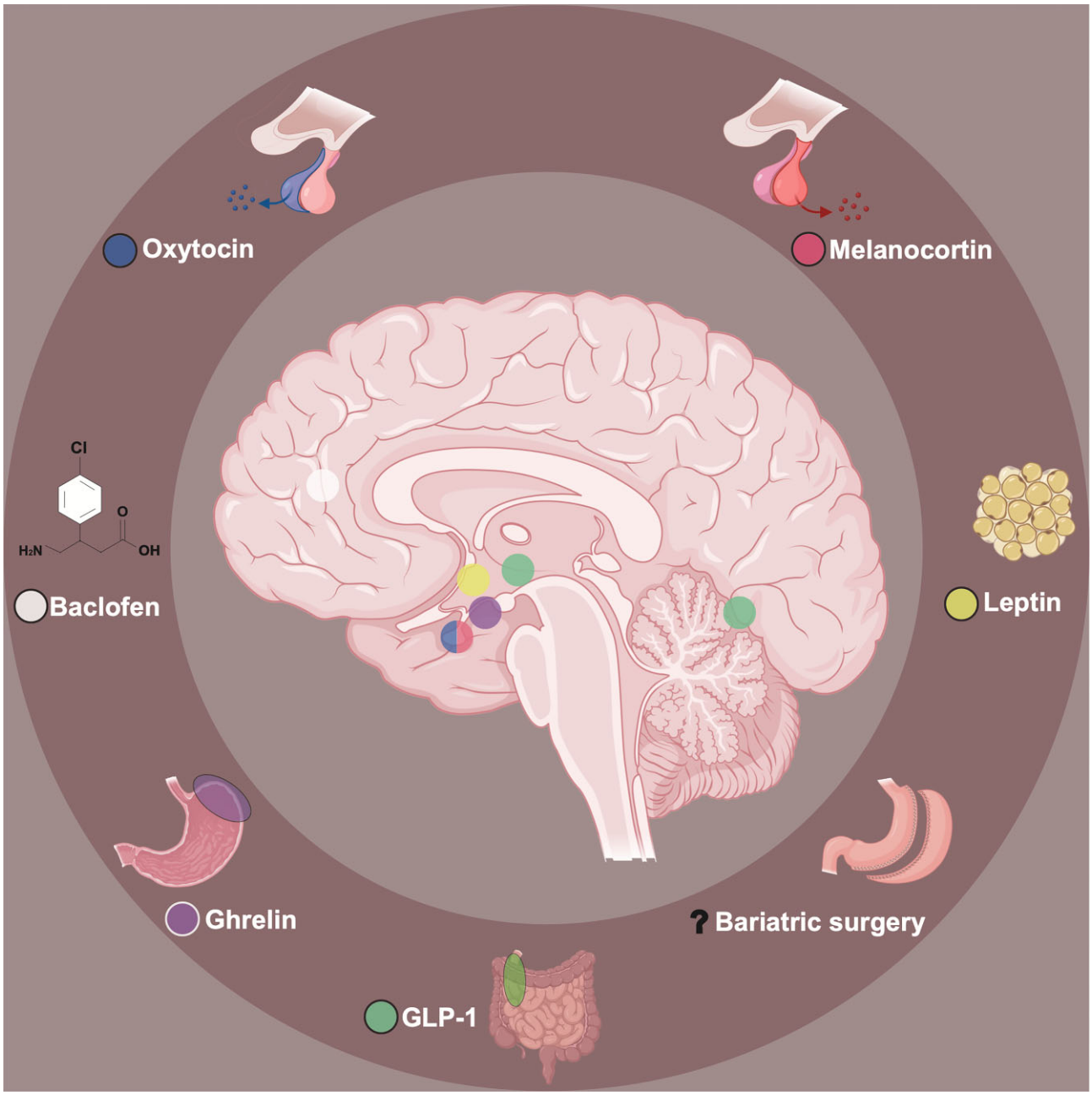

Figure 2: Possible interventions or endocrine-metabolic hormones that may affect food cravings. The figure shows seven potential interventions or hormones that may modulate food cravings, including oxytocin and growth hormone from the hypothalamus-pituitary, leptin from adipose tissue, ghrelin from the stomach, GLP-1 from the duodenum, baclofen, and weight loss metabolic surgery. The inner section of the brain shows the main brain regions that are involved in the neural processing of food cravings, and where the corresponding hormones or drugs may act. Oxytocin and growth hormone mainly act on the hypothalamus-pituitary, ghrelin and leptin also act on different nuclei of the hypothalamus, GLP-1 is mainly produced by the arcuate nucleus and acts on the striatum and amygdala, baclofen may affect the prefrontal cortex area, and weight loss surgery may affect a large number of endocrine hormones, but the brain regions affected are still unclear. This figure uses material from the BioRender website (www.biorender.com/).

nucleus, leading to increased appetite and craving (Lu *et al.*, 2002; Millington, 2007). An experiment discovered that when 26 healthy male and female volunteers viewed images of food and control images, fMRI scans revealed that specific areas of the brain were activated in response to food cues, including bilateral networks in the middle and superior temporal gyrus for visual processing, the caudate nucleus, pallidum, and midbrain for reward, taste-related regions such as the insular and parainsular regions, and the right hypothalamus. The result also showed a positive correlation between fasting levels of Ghrelin and these reactivity to food cues (Kroemer *et al.*, 2013). Moreover, Ghrelin stimulates the cleavage of POMC to adrenocorticotropic hormone (ACTH) in somatotropic cells located in the anterior pituitary through CREB-mediated prohormone convertase-1 gene expression and promotes corticotropin cell proliferation and hypertrophy to enhance the synthesis and secretion of somatotropic ACTH (Arvat *et al.*, 2001), which is likely to lead to stress-related obesity (van Loenen *et al.*, 2022). Fasting plasma levels of ghrelin decrease in obese

participants and increase as a result of weight loss induced by dietary interventions. As obesity leads to elevated fasting insulin levels, the inhibitory effect of insulin on ghrelin secretion may contribute to the modulation of ghrelin's impact on the weight loss process (Tschöp *et al.*, 2001). One study indicates that cigarette smokers have significantly elevated plasma concentrations of the appetite-stimulating peptide acylated ghrelin compared to non-smokers. This elevation in ghrelin levels during the early stages of withdrawal from tobacco might be one of the reasons for increased appetite and subsequent weight gain observed post-cessation, suggesting smokers might compensate these effects by increasing tobacco intake (Koopmann *et al.*, 2015).

Melanocortin

Melanocortin have also been found to increase the brain's sensitivity to food cues. The melanocortin family comprises three forms of melanocyte-stimulating hormone (α-, β-, γ-MSH) and ACTH. These peptide hormones are derived from the proteolytic cleavage of the precursor protein POMC and play crucial roles in various physiological processes, including pigmentation, energy homeostasis, inflammation, and immune responses (Wisse & Schwartz, 2001). Sequencing the potential genes related to obesity in Labrador retriever dogs revealed a 14 base pair deletion in the *POMC* gene, which disrupts the coding sequences for β-MSH and β-endorphin, and is linked to body weight (with a per allele effect of 0.33 standard deviations), increased adiposity, and a higher food motivation (Raffan *et al.*, 2016). Some researchers found Alpha-MSH has some therapeutic potential to control obesity, which can reduce the excess fat and lean mass found in $Pomc^{-/-}$ mice, mediated largely through an effect on food intake (Tung *et al.*, 2006). In an experiment that also used palatable food as a stimulus to evaluate food cravings, obese controls showed reduced activation of the dorsal and ventral striatum compared to MC4R (Melanocortin 4 receptor)-deficient patients and lean controls (van der Klaauw *et al.*, 2014).

Glp-1

GLP-1 not only plays a regulatory role in normal appetite and feeding behavior but may also affect food cravings (De Silva *et al.*, 2011; Zanchi *et al.*, 2017). GLP-1 is a peptide hormone secreted by the intestinal cells that plays a crucial role in the regulation of appetite during feeding (Lovshin & Drucker, 2009). When blood glucose levels are high, GLP-1 increases insulin secretion while inhibiting glucagon release. It also slows down gastric emptying, enhances satiety signals, reduces appetite, and limits food intake by acting on the central nervous system through the vagus nerve. These effects lead to a reduction in blood glucose and body weight, making GLP-1 a promising therapeutic target for metabolic disorders such as type 2 diabetes and obesity (Zhang *et al.*, 2022). A clinical study demonstrated that subcutaneous injection of the GLP-1 receptor agonist semaglutide at a dose of 2.4 mg per week for 20 weeks significantly reduced appetite, leading to a 35% reduction in ad libitum energy intake and a consequent 10% reduction in overall body weight (Friedrichsen *et al.*, 2021). GLP-1 not only functions as an endogenous gut hormone involved in the regulation of body weight in the peripheral circulation but also acts as a neurotransmitter within the central nervous system. GLP-1 receptors are also widely distributed throughout the central nervous system, including the amygdala, where they are highly expressed (Jensen *et al.*, 2018). Peripheral GLP-1 receptor agonists can act on central GLP-1 receptors via the blood–brain barrier, reducing feeding behavior (López-Ferreras *et al.*, 2018), while decreasing central nervous system GLP-1 receptor expression or inhibiting its function increases food intake in mice (Hsu *et al.*, 2018). Furthermore, using neuroimaging techniques, studies have shown that obese patients with and without diabetes exhibit increased brain responses to food pictures in appetite- and reward-related brain regions, such as the insula and amygdala, compared to normal participants. GLP-1 receptor agonist exenatide can reduce food intake and food-related brain responses in type 2 diabetes and obese patients (insula, amygdala, caudate nucleus, and orbitofrontal cortex) compared to placebo (van Bloemendaal *et al.*, 2014). Owing to the lack of research on the underlying neural circuits of GLP-1's effects on food cravings, more evidence is needed to demonstrate the role of GLP-1 receptor agonists in inducing weight loss through their impact on food cravings.

Oxytocin

Oxytocin not only reduces the brain's responsiveness to food cravings but also diminishes significant attentional biases toward food images. Oxytocin (OT) is a naturally occurring peptide hormone and neuropeptide in mammals that is primarily used for the induction of labor through intravenous injection, as it stimulates uterine contractions (Alfirevic *et al.*, 2016). Central and peripheral oxytocin release is triggered by food taking (Blevins & Ho, 2013), and the increase in endogenous oxytocin is involved in reducing anxiety, terminating feeding, and restricting meal size (Meyer-Lindenberg *et al.*, 2011).

A clinical trial demonstrated that the administration of intranasal oxytocin in individuals who were instructed to engage in mental imagery of the consequences of consuming high-calorie foods led to a significant decrease in food cravings compared to the placebo group, by strengthening activity in a broad neurocircuitry implicated in top-down control and self-referential processing (Striepens *et al.*, 2016). A 2022 meta-analysis also demonstrated that a single dose of intranasal oxytocin resulted in a significant reduction in food intake among non-psychiatric participants (Chen *et al.*, 2021). Reaction times to probe stimuli that appeared after the offset of the visual images indicated a significant attentional bias to food pictures after placebo; this effect was significantly attenuated by oxytocin, $P < 0.001$ (Burmester *et al.*, 2022). Consuming food is one of the few primary reinforcers that can activate the mesolimbic reward pathway without requiring prior conditioning. Nevertheless, the release of dopamine in the nucleus accumbens and striatum is diminished by oxytocin, leading to a reduction in the motivation for pleasurable food consumption (McGregor & Bowen, 2012), which needs to conduct further investigation to dig more into the mechanism.

Baclofen

Although Baclofen has been associated with food cravings, no effective neuroimaging results specifically related to food cravings tasks have been discovered. Baclofen, an agonist of the γ-aminobutyric acid B receptor, has been used as a prominent antispasticity agent since the 1970s (Dralle *et al.*, 1985). In individuals who self-report binge eating, a daily dose of 60 mg of titrated baclofen significantly reduces food cravings, as measured by a decrease in Food Cravings Inventory-II scores (Corwin *et al.*, 2012). Baclofen has been proposed as a potential pharmacotherapy for alcohol use disorder and alcohol craving (Farokhnia *et al.*, 2021), but conflicting clinical data exist (Farokhnia *et al.*, 2017). The efficacy of baclofen in reducing food cravings requires extensive experimental data to establish its effectiveness.

Bariatric surgery

Weight loss surgery is experiencing a global increase in popularity, with two predominant types known as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy, which has been confirmed to be associated with food cravings through various imaging techniques. These two procedures individually account for >200 000 surgeries annually (Angrisani *et al.*, 2021). Patients who have undergone bariatric surgery commonly report reductions in hunger, earlier satiety, and changes in food preferences (Halmi *et al.*, 1981). Some studies have found that post-surgery patients exhibit a decrease in total energy intake, a selective reduction in high-fat and high-carbohydrate intake, and an increased sensitivity to sweetness, which is perceived as stronger. The attractiveness of sweet and fatty foods is reduced, and fMRI studies show a corresponding decrease in activation of the brain reward center to high-energy food cues (Behary & Miras, 2015; Dixon *et al.*, 2005). In some cohorts comprising multiple obese individuals and a control group, assessments were conducted one month after undergoing laparoscopic sleeve gastrectomy (LSG). These studies revealed a significant reduction in fasting plasma concentrations of total ghrelin, leptin, and insulin following LSG, as well as decreases in appetite and altered brain responses to high-calorie food cues, particularly in the right DLPFC (Li *et al.*, 2019; Zhang *et al.*, 2019). Simultaneously, using high-calorie and low-calorie food images to investigate brain responses one month after LSG surgery, it was observed that LSG significantly reduced activation in the right DLPFC in response to high-calorie compared to low-calorie cues. Additionally, there was an augmentation in functional connectivity between the DLPFC and the ventral anterior cingulate cortex, both of which are regions implicated in the self-regulation of feeding behavior (Hu *et al.*, 2021, 2020). A neuroimaging study using positron emission tomography found that participants who underwent RYGB had higher overall satiety and food-induced sickness, as well as lower ad libitum intake after overnight fasting. The growth hormone inhibiting hormone in RYGB reduced postprandial peptide responses and activation in medial orbital cortex (Hunt *et al.*, 2016). Neurological changes also suggest that weight loss surgery improves the inhibition of responses to high-energy food cues, and changes the impact of metabolic control during the inhibition of responses to low-energy food cues. Alterations in neural circuits involved in inhibitory control, satiety signaling, and reward processing may contribute to the effective weight loss observed after RYGB (Zoon *et al.*, 2018). The study underscores the significance of neural activity in reward-associated circuits, such the nucleus accumbens, as robust indicators of weight loss outcomes post-bariatric surgery. Notably, the baseline brain responses when desiring palatable foods outperformed traditional behavioral and hormonal predictors in forecasting 12-month post-operative weight reductions (Holsen *et al.*, 2018).

Future direction

Neuroendocrine perspective

Food cravings, deeply rooted in both trait and state components, are characterized by individual preferences, varying notably with the day's cyclical variations and distinctive physiological cycles in females, such as menstruation and pregnancy. Exploring this aspect might illuminate effective interventions, highlighting the connection between cravings, obesity, and the neuroendocrine system. By introducing a neuroendocrine perspective, we hope to examine the fact that food craving is a complex psychological trait that has both trait and state components, and that there are individual food preferences that vary with the endocrine system, typically characterized by cyclical variations throughout the day, as well as variations in the physiological cycle of the female physiology and during pregnancy. By delving deeper into this perspective, future research might yield more targeted and effective interventions, shedding more light on the nexus of cravings, obesity, and the neuroendocrine system.

Consideration of psychiatric disorders

Food cravings and appetite discrepancies in obese individuals might be intensified by accompanying psychiatric conditions. It is important to note that food cravings and appetite problems in the obese population discussed in this study may be influenced by concomitant psychiatric disorders (Kroemer *et al.*, 2022; Platzer *et al.*, 2020). For instance, disorders such as depression and anxiety, which are linked to obesity and abnormal eating patterns, can significantly modulate appetite and cravings through various mechanisms (Andréasson *et al.*, 2007; Simmons *et al.*, 2020). Ensuring clarity in research findings demands that future studies implement stringent exclusion criteria or employ statistical matching methods.

Clinical interventions and their implications

The insights provided by this review might shape obesity interventions. Key points include refining dietary structures, emphasizing the balance of the endocrine system, innovating precise food craving assessment tools, and endorsing a multidisciplinary approach. The results of the present review may provide some insights into comprehensive clinical interventions for obesity. First, optimizing the dietary structure from a holistic perspective, not only focusing on fat intake, but also emphasizing the proportion of protein and carbohydrates, and increasing the proportion of saturated foods, which may help to regulate appetite and food cravings. Second, great attention should be paid to the balance of the endocrine system, and hormone levels should be regulated by pharmacologic or non-pharmacologic means. Third, more accurate food craving assessment tools should be developed, supplemented by functional imaging indicators to monitor the response to intervention. Finally, the importance of multidisciplinary teamwork is emphasized, with experts in the fields of medicine, nutrition, psychology, and nursing working together to design individualized and comprehensive treatment plans, which are expected to achieve better outcomes.

New therapeutic frontiers

Therapeutic innovations such as lorcaserin and its combination with phentermine, VLCK (Very Low-Calorie Ketogenic) diets, and interventions such as deep transcranial magnetic stimulation (dTMS), are emerging as potential game-changers in obesity management. Each of these approaches addresses different facets of food cravings and obesity, offering a multifaceted way forward.

A study involving 137 adults after a low-calorie diet phase examined the combined effects of lorcaserin and behavioral therapy. While the lorcaserin group showed enhanced handling of emotions and stress-related eating compared to the placebo group, food cravings remained relatively consistent between the two (Chao *et al.*, 2018). For a lorcaserin and phentermine combination, an extension of the lorcaserin research, when combined with

Phentermine over a 12-week span, manifested a notable control over cravings. This combination outperformed lorcaserin alone, showcasing its effectiveness in curbing both general and specific food cravings (Rebello *et al.*, 2018). Regarding nutrient intake and hunger modulation, two intriguing pilot studies dived into oral nutrient intake rates and intravenous macronutrient applications. They discerned that food volume combined with the energy intake rate in standard consumption significantly affected satiety. By contrast, slow nutrient intake or low-rate intravenous applications lacked this effect, thus emphasizing the dual role of food volume and energy rate in hunger and appetite regulation (Denzer-Lippmann *et al.*, 2017). Delving into the VVLCK diet's potential, research indicated its efficacy in modulating food and alcohol cravings, sleep patterns, physical activity, and the overall quality of life in obese patients. The VLCK diet's rapid effects on weight and fat mass reduction hinted at its potential as a long-term therapeutic strategy, linking better food control and enhanced psychological health (Castro *et al.*, 2018). In rsearching dTMS, non-invasive brain stimulation surfaced as an enticing avenue for addressing cravings. A study with 45 obese participants showcased the prowess of high-frequency dTMS in curtailing impulsivity and inducing weight reduction, pointing toward its role in amplifying the prefrontal cortex's inhibitory capacity and modulating the neuroendocrine system, notably influencing leptin levels (Luzi *et al.*, 2021). In essence, these burgeoning therapeutic avenues highlight the evolving landscape of obesity management, underlining the need for integrated approaches to tackle the multifaceted challenges of food cravings and obesity.

In conclusion, food cravings, distinct from appetite, are shaped by individual preferences and are intricately tied to one's psychological state. A holistic exploration of this subject, incorporating factors such as ghrelin, leptin, and various neuro-endocrine mechanisms, is paramount (Krishnan *et al.*, 2016) (Parker *et al.*, 2021) (Moeller *et al.*, 2016). As we venture further, incorporating both the biological and behavioral intricacies of this phenomenon into interventions will be vital. It is essential to note that this study used a narrative literature review approach, emphasizing a holistic overview rather than a systematic evaluation of a specific clinical problem.

Author contributions

Jin Huang (Writing – original draft), Chen Wang (Investigation), Hang-Bin Zhang (Writing – review & editing), Hui Zheng (Conceptualization, Visualization), Tao Huang (Resources), and Jian-Zhong Di (Supervision)

Conflict of interest

The authors declare that no conflict of interests exist.

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