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Neuromodulation for the treatment of eating disorders and obesity

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Abstract: Eating disorders and obesity adversely affect individuals both medically and psychologically, leading to reduced life expectancy and poor quality of life. While there exist a number of treatments for anorexia, morbid obesity and bulimia, many patients do not respond favorably to current behavioral, medical or bariatric surgical management. Neuromodulation has been postulated as a potential treatment for eating disorders and obesity. In particular, deep brain stimulation and transcranial non-invasive brain stimulation have been studied for these indications across a variety of brain targets. Here, we review the neurobiology behind eating and eating disorders as well as the current status of preclinical and clinical neuromodulation trials for eating disorders and obesity.

Keywords: anorexia nervosa, bulimia, deep brain stimulation, eating disorders, non-invasive brain stimulation, obesity, transcranial direct current stimulation, transcranial magnetic stimulation

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Introduction

Eating disorders and obesity are characterized by abnormal and detrimental eating habits, and often result in significant medical and psychiatric comorbidities. They are associated with reduced quality of life and life expectancy.[1–3] In many ways, morbid obesity and anorexia nervosa (AN) represent extremes on two ends of the eating spectrum. Morbid obesity is defined as a body mass index (BMI) greater than 40 kg/m^2 (or greater than 35 kg/m^2 in the presence of a significant obesity-related comorbid condition), while AN is defined by an extremely low BMI (<18.5 kg/m^2) and concomitant anxiety and preoccupations related to weight and body image. Both diseases exert a significant individual and societal impact, albeit in different ways. Morbid obesity is a chronic, progressive disease with a prevalence of approximately 14%, and associations with comorbidities including cardiovascular disease, type 2 diabetes mellitus, osteoarthritis and various cancers.[4,5] By contrast, only 0.7–3% of the population (with a 10:1 predominance in the female population) suffers from AN, but this disease is also associated with critical metabolic, endocrine and electrolyte imbalances, psychiatric comorbidities and an even higher risk of mortality due to suicide or medical complications (5–15% mortality rate).[6–9] Bulimia nervosa (BN), a similar but distinct eating disorder characterized by recurrent episodes of binge-eating and inappropriate compensatory behaviors, is estimated to have an overall prevalence of 0.3% and may afflict as many as 1% of young women.[10,11] It too is often functionally debilitating and accompanied by psychiatric comorbidities and linked to increased mortality.[12]

There is a need for additional treatment modalities in both obesity and eating disorders. Current treatments for obesity vary in efficacy and invasiveness, ranging from conservative measures (diet, exercise, cognitive behavioral therapy)[13,14] to medications (e.g. benzphetamine, orlistat, rimonabant)[15] and bariatric surgery (Roux-en-Y gastric bypass, laparoscopic adjustable gastric band, sleeve gastrectomy, vertical band gastroplasty).[16] Of these options, bariatric surgery is the most effective treatment for rapid weight loss but is still associated with an approximately 10–27%

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failure rate.[17,18] Cognitive behavioral therapy (CBT), selective serotonin reuptake inhibitors (SSRIs) and neuroleptics constitute the mainstay treatments for AN at present. The efficacy of these treatments, however, is fairly poor and up to 30% of AN patients prove to be medically intractable.[19] The situation is similar for BN; patients are typically treated with CBT[20] and/or antidepressant pharmacotherapy,[21] but the majority of patients remain symptomatic following therapy.[22]

Deep brain stimulation (DBS) is an invasive but non-lesional neurosurgical procedure that delivers electrical pulses to targeted brain structures via electrodes connected to an implantable pulse generator (IPG). It is well established as a safe and efficacious treatment for movement disorders such as Parkinson's disease, dystonia and tremor,[23] presenting a more flexible approach compared to lesioning treatments owing to its reversibility and modifiability. More recently, DBS has shown promise as a potential treatment for several circuit-based neuropsychiatric conditions, including obsessive-compulsive disorder (OCD),[24,25] major depression,[26,27] Tourette's syndrome,[28,29] and Alzheimer's disease.[30,31] It has also been explored for use in eating disorders such as morbid obesity and AN.

By contrast, non-invasive brain stimulation (NIBS) involves transcranial stimulation of cortical neural targets in a non-surgical manner. Of the many different NIBS modalities that exist, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are among the most popular and frequently studied. Each differs in terms of its mechanism of stimulation; rTMS passes brief current pulses through a coil over the scalp in order to generate an electromagnetic field that inhibits (low frequency, <5 Hz rTMS) or activates (high frequency, >5 Hz rTMS) target neurons,[32] while tDCS delivers weak electrical current to brain regions through electrodes placed on the scalp in order to either depolarize (anodal tDCS) or hyperpolarize (cathodal tDCS) resident neurons.[33] Both rTMS and tDCS have been explored with varying success for a multitude of indications, including OCD,[34,35] depression,[36,37] anxiety,[38,39] chronic pain,[40,41] stroke rehabilitation[42,43] and addiction.[44,45] They too have been applied to eating disorders and obesity.

Here, we review the theoretical rationale and current results of DBS and NIBS for eating disorders and obesity.

Neurobiology of eating behavior: homeostatic and reward pathways

While the neural basis of eating behavior is not fully understood, it has been linked to an interaction between reward pathways (mesolimbic and mesocortical pathways; Figure 1) and homeostatic circuitry that regulates an individual's perceived dietary energy needs. Certainly, the hypothalamus is well-recognized to play an integral role in maintaining homeostasis with regards to energy balance, constituting a key junction between the endocrine and nervous systems via its responsiveness to gut and adipocyte-derived hormones, integration of multimodal feeding-related sensory signals and close connections with brainstem regions (such as the nucleus of the solitary tract) involved in autonomic monitoring.[46] The importance of hypothalamic control over eating behavior is further evinced by the consequences of lesioning this region, which variably include secondary anorexia[47,48] and secondary obesity.[49] Informed by rodent studies in the 1950s and 1960s, the hypothalamus was classically envisioned as regulating eating behavior through competing 'feeding' (lateral hypothalamus) and 'satiety' (ventromedial hypothalamus) centers that, when lesioned or stimulated, dramatically altered food intake patterns. Specifically, lateral hypothalamus lesions resulted in severe aphagia, food aversion and weight loss, while ventromedial lesions led to voracious, uncontrolled eating and weight gain.[50,51–53]

While these early experiments have since been deemed somewhat imprecise, this 'dual center model' has nonetheless held up well as a basic schema of hypothalamic control over appetite.[54] The lateral hypothalamus is the only region in the brain containing neurons that produce orexins, a peptide implicated in hunger and arousal. Indeed, dysregulation or loss of orexin signaling has been associated with obesity.[55] In contrast, the ventromedial hypothalamus contains a high number of leptin receptors, which are involved in satiety. In mice, high levels of leptin are usually associated with reduced feeding, while animals with low leptin levels tend to eat uncontrollably.[56]

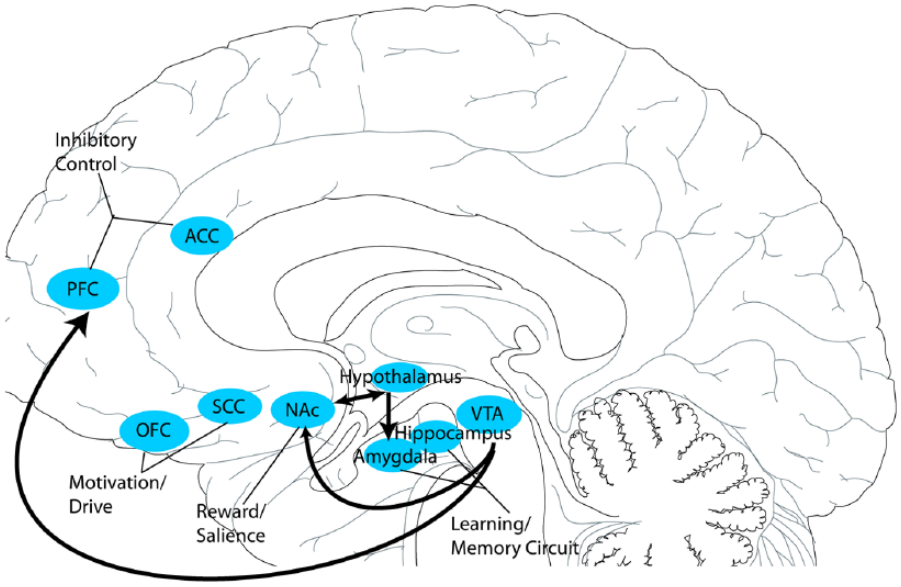

Figure 1. Reward pathways and interactions. This schematic illustrates the hypothalamic–mesocorticolimbic pathways and potential anatomical targets involved with reward, cognitive control, motivation and the learning/memory circuits. Reward and saliency involve the ventral tegmental area, nucleus accumbens and caudate. The orbitofrontal cortex and subgenual cingulate cortex are thought to be involved in motivation and drive. The learning/memory circuit, which includes the amygdala, hippocampus and putamen, are also components in eating neurobiology. Inhibitory control has been known to involve the dorsolateral prefrontal cortex, ventromedial prefrontal cortex, and the anterior cingulate cortex. The arrows signify the direction of signal transmission.
ACC, anterior cingulate cortex; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PFC, prefrontal cortex; SCC, subgenual cingulate cortex; VTA, ventral tegmental area.

Reward circuitry – in particular the mesolimbic and mesocortical pathways – also play a key role in governing eating behavior. The mesolimbic reward pathway is a dopaminergic pathway that runs within the medial forebrain bundle, connecting the ventral tegmental area (VTA) to the nucleus accumbens (NAc)[57] within the ventral striatum. It has long been associated with immediate rewards, and along with other cortical reward areas is consistently activated by palatable foods, drugs of abuse, copulation and other rewarding stimuli.[58–61] Moreover, mesolimbic dopamine release in response to rewarding stimuli is known both to track stimulus salience and novelty and reflect the influence of expectation and reinforcement, underlining its role in motivation, want and addiction.[62,63] Unlike the hypothalamus, the NAc is believed to instantiate the value of stimuli like food, regardless of appetite or satiety.[63,64] More specifically, rodent studies indicate the existence of a rostral 'hotspot' in the NAc shell where GABAergic and glutamatergic activation produces appetitive behaviors, while the same neurotransmitters administered in a more caudal 'coldspot' result in fearful or defensive behaviors.[65,66] By contrast, the mesocortical pathway, which comprises dopaminergic output from the VTA to the prefrontal cortex (PFC), is heavily implicated in instantiation of delayed reward, cognitive control, motivation and regulation of emotional responses.[67] Moreover, human imaging studies suggest that the PFC and mesocortical pathway are specifically involved in regulating food intake.[68]

It is important to note the close structural and functional interconnectivity between homeostatic circuitry and reward pathways in the brain. The mesolimbic pathway, for instance, is closely connected to the hypothalamic areas via the inferomedial branch of the medial forebrain bundle.[69] It is also understood that orexins originating in the lateral hypothalamus modulate VTA and mesolimbic pathway activity.[70,71] The relevance of this orexin regulation to behavior is borne out by rodent studies that revealed orexin receptor blockade reduces both interest in and NAc dopamine release response to drugs of abuse.[72–74]

Anatomical targets for obesity

When deciding on a neuromodulation target for obesity, there are multiple aspects of overeating that can potentially be treated. Different parts of the brain regulate motivation, volitional control, addiction, memory and reward. Moreover, it is important to determine if the goal is to increase metabolism, reduce the pleasure/addiction to eating and/or influence an individual's decision-making and volitional control.

Hypothalamus

On the basis of aforementioned lesion studies in rodents, felines, canines, porcines and non-human primates,[50–52,75–77] the hypothalamus has long been an attractive DBS target for obesity. Specifically, high-frequency stimulation (180–200 Hz) of the lateral hypothalamus has been shown to reduce feeding and produce sustained weight loss in rodent and primate DBS models.[78,79] It also appears to result in increased metabolism in the hippocampus, amygdala and mammillary body.[80] In contrast, low-frequency (50 Hz) lateral hypothalamus stimulation increased feeding.[81–83] The opposite pattern occurred when targeting the ventromedial hypothalamus; here, high-frequency stimulation caused weight gain in rodent and primate models,[84,85] while low-frequency stimulation promoted weight loss.[77] Interestingly, as orexin deficiency is associated with obesity, driving this pathway may help to prevent and treat obesity.[55]

Nucleus accumbens

Obesity is a multifactorial disease that involves altered patterns of eating and satiety as well as dysfunctional reward and compulsive traits.[86] Several models emphasize the role of dopaminergic reward circuits, with each proposing a different account of the specifics of the abnormality and how it relates to overeating.[87] The reward surfeit model posits that those at risk for obesity have a greater reward responsivity in the gustatory and somatosensory cortex.[88] Indeed, there is evidence that an elevated responsiveness of reward-related regions may portend a poor outcome in weight-loss programs.[89] The incentive sensitization model suggests that repeated food intake leads to an elevated responsivity to foods due to conditioning.[90] The reward deficit model posits there is lower brain dopamine activity in obese subjects, predisposing them to excessive eating.[91]

Animal models have demonstrated that lesioning the NAc eliminates food-hoarding behavior and promotes weight loss.[92] High-frequency stimulation (160 Hz, 60 μs pulse width) of the lateral NAc shell in obese rats was noted to increase D2 receptor gene expression and DA levels and result in weight loss; however, there was no change in normal-weight rats.[93] Interestingly, stimulation (130 Hz, 60 μs pulse width) of the medial NAc shell increased feeding.[94] Furthermore, animal studies have demonstrated that bilateral high-frequency NAc stimulation reduces binge-eating.[95]

Other targets for obesity

There are many other potential DBS targets for obesity beyond the lateral hypothalamus and NAc. One study comparing fMRI BOLD activity in response to pictures of food between obese participants and healthy controls observed significantly greater activation in the obese group, not only in NAc/ventral striatum, but also in medial and lateral orbitofrontal cortex, medial PFC, insula, anterior cingulate cortex, amygdala, ventral pallidum, caudate, putamen and hippocampus. In contrast, there was decreased hypothalamic and dorsal anterior cingulate cortex activation in the obese cohort.[96] Other work has found evidence of decreased PFC and striatum metabolism with correlating alterations in dopamine in obese individuals.[59]

Clinical DBS trials for obesity

Hypothalamus

Informed by promising preclinical data, lesioning experiments were performed on the lateral hypothalamus in the 1970s with the intent to break the reward cycle for eating. These studies demonstrated initial weight loss in obese patients; after 1 year, however, treated patients regained the weight.[97,98] Nonetheless, this work provided further support for trials exploring neuromodulation of the homeostatic system.

In 2008, bilateral ventromedial hypothalamus stimulation for obesity was performed (Table 1). In this case report of a 50-year-old man with morbid obesity, high-frequency (130 Hz) stimulation did not alter the patient's overall weight. However, low-frequency (50 Hz) stimulation resulted in initial weight loss followed by weight gain. These results were confounded by the patient turning off the stimulation at night in order to eat during

Table 1. DBS for morbid obesity patients. This table illustrates six reports of DBS for obesity. Four female patients and two male adult patients underwent DBS targeting either the hypothalamus or the nucleus accumbens. Four out of the six patients exhibited a reduction in their BMI after DBS.

Study	Target	Stimulation parameters	Number of patients	Age	Gender	Initial BMI	BMI after DBS	Follow up (months)	Comorbidities
Hamani and colleagues[30]	Ventral hypothalamus	130, 50 Hz, 60 µs pw, 2.8 V	1	50	Male	55	–	5	DM2, HTN, OSA
Whiting and colleagues[101]	Lateral hypothalamus	185 Hz, 90 µs pw	3	45–60	2 female, 1 male	45–49	(1) 0.9% decrease, (2) 12.3% decrease, (3) 16.4% decrease	30–39	(1) HTN; (2) OSA/DM2, HTN, migraine; (3) lower extremity edema
Mantione and colleagues[102]	NAc	185 Hz, 90 µs pw, 3.5 V	1	47	Female	37	25	24	OCD
Harat and colleagues[103]	NAc	130 Hz, 208 µs pw, 2 mA	1	19	Female	53	48	14	Cranipharyngioma

DBS, deep brain stimulation; DM 2, type 2 diabetes mellitus; HTN, hypertension; NAc, nucleus accumbens; OSA, obstructive sleep apnea; pw, pulse width.

the latter part of the trial, suggesting DBS may have affected the patient's appetite but not overall desire to eat.[30] High-frequency stimulation of ventromedial hypothalamus has resulted in interesting side effects other than weight loss. In one case report, stimulation led to memory benefits,[30] while a second case report indicated that stimulation induced panic attacks.[99] The failure of ventromedial hypothalamic stimulation may be due to redundant mechanisms in the hypothalamic-mediated regulation of feeding. Alternatively, stimulation may shut down both orexigenic and anorexigenic mechanisms via current spread to the neighboring lateral hypothalamus.[100] This preliminary result was followed by a small, three-patient case series of bilateral lateral hypothalamic DBS in failed gastric bypass patients. High-frequency monopolar (185 Hz, 90 µs pulse width) stimulation was used with no adverse effects at 35 months. Resting metabolic rate was also measured using indirect calorimetry in a respiratory chamber, and was found to be augmented by DBS. While no improvement in weight was observed when DBS parameters were programmed to standard (movement disorder-informed) settings, stimulation programmed to optimize resting metabolic rate was associated with weight loss in two of three patients. Resting metabolic rate-optimized stimulation was also linked to subjective reports of decreased urge to eat and increased energy levels.[101]

Nucleus accumbens

In addition to targeting the homeostatic center, clinical studies have also utilized DBS to stimulate the mesolimbic pathway – specifically the NAc. In two separate case reports, bilateral NAc DBS resulted in weight loss and a reduction in BMI.[102,103] In the first case, a woman suffered from obesity and obsessive compulsive disorder. Bilateral NAc stimulation (185 Hz, 90 µs pulse width) resulted in a significant reduction in BMI and weight loss at 2 years after DBS implantation. In the second case, a woman suffered from hypothalamic obesity secondary to a craniopharyngioma status post resection. Chronic bilateral NAc stimulation (130 Hz, 208 µs pulse width) led to a reduction in BMI 14 months after surgery.

Anatomical targets for anorexia nervosa

Insula

AN is an eating disorder characterized by low body weight (<18.5 kg/m^2), fear of gaining weight and a distorted perception of body and self-image. It is often comorbid with affective disorders such as depression or bipolar disorder. Moreover, it is frequently associated with reward processing abnormalities and obsessive habits resembling those seen in OCD behavior.[104–106] Prior imaging studies suggest AN involves dysfunction within a number of neural pathways, including circuitry pertaining to

self-awareness (parietal cortex, insula), visual and gustatory sensation (occipital cortex and insula) and reward (ventral striatum, anterior and subcallosal cingulate, dorsolateral PFC and ventromedial PFC).[59,107–109] The insula, which subserves interoception (an individual's self-observation of the body's internal homeostasis), is implicated in many of these circuits and may particularly relate to distorted perceptions in AN.

Ventral striatum/nucleus accumbens

One theory of AN pathogenesis suggests there exists an imbalance in serotonergic signaling within the ventral striatum, perhaps related to the aversion aspect of the disorder.[110] Another theory is that there are perturbations in the reward pathways.[111–113] Disrupting the dopamine system can affect the reward circuitry, leading to a dysphoric mood and anxiety.[6,114] There is evidence of a dopamine imbalance in the ventral striatum.[110] AN patients have been found to exhibit decreased ventral striatum activity as well as overactivity in the caudate.[115] Furthermore, AN patients' reward pathways are activated by disease-related stimuli, but are not necessarily activated with typical rewarding stimuli. For instance, there is overactivation of the ventral striatum in response to thin, underweight stimuli,[116] unlike in morbid obesity where the ventral striatum is preferentially engaged by eating. Similarly, the ventromedial PFC is significantly more active in AN patients during exposure to high- and low-caloric food items.[117]

Other targets for anorexia

Evidence also exists for dysfunctional decision-making processes in AN patients. In fact, imaging work indicates there is reduced glucose perfusion in decision-making and motor action centers in patients with AN (superior frontal cortex, caudate, thalamus and putamen).[118] Moreover, the anterior cingulate is implicated in AN by the finding that AN patients possess decreased cingulate volume compared to controls, with subsequent enlargement after recovery.[119]

Clinical DBS trials for anorexia nervosa

Ventral striatum/nucleus accumbens

Early case studies in the 1950s suggested that disrupting the reward pathways through limbic leucotomy,[120,121] thalamotomy[122] and capsulotomy[123] could produce benefits in AN patients and prove useful as a last resort for intractable cases. However, the clinical outcomes have been inconclusive. Given evidence of reward pathway disruption in AN, the ventral striatum (and the NAc in particular)[57] has been identified as a potential DBS target for this condition (Table 2). In one study, a cohort of AN patients with comorbid OCD, depression or anxiety underwent stereotactic radiofrequency ablation of the NAc (six patients) or bilateral NAc DBS (two patients; 135–185 Hz). In both treatment groups, BMI as well as comorbid psychiatric symptoms showed improvement after 1 year in conjunction with decreased psychoticism, neuroticism and lying tendencies, and improvements in memory/cognition at 6 months.[124] Another trial examining bilateral NAc DBS (180 Hz) in four AN patients with comorbid OCD or generalized anxiety also demonstrated improvements in BMI.[125] DBS targeting the bilateral ventral capsule/ventral striatum (120 Hz) in a patient with OCD, major depression and AN similarly produced gains in weight and BMI.[119] Importantly, NAc DBS also appears to reverse a number of metabolic abnormalities seen in AN; according to one PET study, hypermetabolism in the frontal lobes, hippocampus and lentiform nucleus was decreased in six AN patients following NAc DBS.[107]

Subgenual cingulate cortex

Another potential target for AN DBS is the subgenual cingulate cortex (SCC), a region with cortical projections to the medial and orbitofrontal cortex and subcortical projections to NAc, which is known to play an important role in mood regulation.[129] The SCC exhibits increased activity and decreased 5-HT_{2A} binding in AN.[130] It also exhibits altered connectivity, with predominance in left-sided abnormalities. More specifically, tractography work has identified increased left parieto-occipital, dorsolateral prefrontal and left cerebellum connectivity, as well as decreased lower thalamic, mid- and anterior cingulate, and left anterior temporal cortices connectivity within the SCC in AN patients. The most conspicuous differences were increased connectivity between the SCC and the ipsilateral parietal cortex and decreased connectivity between the SCC and bilateral thalami.[129] These findings are consistent with dysfunctional affective circuitry in patients with AN. Greater pre-operative deficits in connectivity within the left fornix, inferior frontal occipital cortex and right anterior limb of the internal capsule have been associated with better post-operative DBS affective clinical outcomes.

Table 2. DBS for anorexia nervosa patients. This table illustrates 25 cases of DBS for anorexia nervosa. All 25 patients were adult female patients who underwent DBS targeting the NAc, SCC, VC/VS, or BNST. All of the studies, except for the VC/VS and BNST (no follow up for the VC/VS study, decrease in weight with the BNST study) studies, demonstrated an increase in BMI with DBS.

Study	Target	Stimulation parameters	Number of patients	Age	Gender	Initial BMI	BMI after DBS	Follow up (months)	Comorbidities
Wang and colleagues[124]	NAc	135–185 Hz, 120–210 μs pw, 2.5–3.8 V	2	18–28	Female	12.9–13.3	18–21	12	(1) OCD, depression, anxiety; (2) depression, anxiety
Wu and colleagues[125]	NAc	180 Hz, 90 μs pw	4	16–17	Female	10–13.3	17–22	9–50	(1) OCD; (2) OCD; (3) OCD; (4) Anxiety disorder
Israel and colleagues[126]	SCC	Right-sided: 130 Hz, 91 μs pw, 5 mA	1	52	Female	14.4	19	30	Depression
Lipsman and colleagues,[127] Lipsman *et al.*[128]	SCC	130 Hz, 90 μs pw, 5–6 V	16	34	Female	13.8 ± 1.5	17.3 ± 3.4	12	
McLaughlin and colleagues [119]	VC/VS	120 Hz, 120 μs pw, 7.5 V	1	52	Female	18.5			OCD, depression
Blomstedt and colleagues[129]	BNST	130 Hz, 120 μs pw, 4.3 V	1	60	Female	15.2	14.3	12	

BNST: bed nucleus of stria terminalis; NAc: nucleus accumbens; OCD: obsessive-compulsive disorder; pw: pulse width; SCC, subgenual cingulate cortex; VC/VS: ventral capsule/ventral striatum.

In 2010, Israel and colleagues described a patient with depression and AN who underwent SCC stimulation that resulted in improvement in mood. Here, they implanted bilateral SCC electrodes; however, they only stimulated the right side chronically (130 Hz, 91 μs pulse width). This stimulation resulted in a sustained elevation in her BMI and improvement in depression.[126] In 2013, Lipsman and colleagues completed a phase I clinical trial stimulating bilateral SCC (130 Hz, 90 μs pulse width) in six patients, finding improvement in mood, anxiety, anorexia-related obsessions and compulsions in two-thirds of the patients. More recently, Lipsman and colleagues published their open-label 1-year follow up on 16 patients (including the initial six patients) with SCC stimulation for AN. In this cohort, 14 of the 16 patients had mood disorders, anxiety disorders or both. Here, they reported sustained improvements in BMI and affective symptoms in some of the patients without significant side effects. Significant changes in cerebral glucose metabolism were also noted in AN-related regions (decreased metabolism: SCC, anterior cingulate; increased metabolism: parietal lobe).[127,128] The most common adverse event was pain related to the incision site. Two of the 16 patients had their DBS system removed or deactivated due to poorly defined reasons.

Bed nucleus of stria terminalis

Yet another stimulation target currently under investigation for AN is the stria terminalis, a key output channel for the amygdala connecting to the hypothalamus. The bed nucleus of the stria terminalis (BNST) in particular is implicated in threat monitoring,[132] and has been proposed to play a part in an anxiety-regulating network comprising the amygdala, hypothalamus, thalamus and orbitofrontal cortex[133] that is closely modulated by serotonergic activity.[134] A recent case report found that bilateral BNST stimulation (130 Hz, 120 μs pulse width) in a patient with major depressive disorder and AN resulted in improvement in depression and anxiety (including anxiety about food and eating) after 1 year, but without any concomitant BMI changes.[129]

Non-invasive brain stimulation for eating disorders

NIBS modalities such as rTMS and tDCS have also been explored for the treatment of obesity and eating disorders. Building on promising work in psychiatric indications such as depression and addiction,[36–39,44,45,135] NIBS methods have typically targeted the PFC in the context of disorders of eating behavior. As a key node of the brain's frontostriatal cognitive circuits, the PFC – particularly the dorsolateral PFC (dlPFC) – is known to underpin executive functions such as inhibitory cognitive control.[136,137] Furthermore, its activity has been closely linked to self-control in a dietary context.[68] The PFC is also implicated in higher-order reward processing as part of its involvement in the mesocortical dopaminergic pathway.[138] Indeed, dopaminergic signaling within the PFC has been linked to regulation of food intake.[139]

NIBS for obesity

In line with this schema, studies examining the effect of single-session dlPFC NIBS in healthy participants who endorsed food cravings consistently found stimulation reduced cravings in the immediate aftermath of stimulation.[140–144] However, a recent meta-analysis established that these single-session effects did not translate into a significant effect on food consumption.[145] A total of eight trials have thus far explored the effect of dlPFC NIBS in overweight or obese participants (Table 3). An initial randomized, blinded trial explored the impact of single-session bilateral dlPFC (2 mA, 20 min, anodal right dlPFC stimulation and cathodal left dlPFC stimulation) tDCS in 19 participants, finding stimulation decreased food cravings but not food consumption during subsequent same-day testing.[142] However, only 11 of 19 participants were overweight or obese, and no outcomes were reported for the overweight/obese cohort specifically. As such, the validity of these findings with respect to obese individuals is uncertain. In an ensuing randomized controlled trial of nine overweight participants, Montenegro and colleagues found that a single session of left dlPFC anodal tDCS (2 mA, 20 min) reduced appetite and desire to eat during immediate post-treatment testing.[146] Subsequently, a double-blind, randomized, placebo-controlled crossover experiment found that three sessions of anodal tDCS (2 mA, 40 min) targeting left dlPFC led to reduced caloric consumption (as well as greater weight loss over the three-day study period) in nine overweight/obese participants following completion of stimulation. However, this finding only proved statistically significant when anodal stimulation was compared with inhibitory cathodal stimulation (not when anodal stimulation was

Table 3. NIBS (rTMS and tDCS) for obesity patients. This table illustrates 31 cases of transcranial direct current stimulation and 13 cases of repetitive transcranial magnetic stimulation for obesity.

Study	Modality	Target	Stimulation parameters	Stimulation timing	Number of patients	Age	Outcome	Follow up (effect duration)
Goldman and colleagues[142]	tDCS	Bl dlPFC	2 mA, anodal (R dlPFC), cathodal (L dlPFC)	Single 20-min session	19*	32.5 ± 11	Decreased food cravings but not food intake	None (unknown effect duration)
Montenegro and colleagues[146]	tDCS	L dlPFC	2 mA, anodal	Single 20-min session	9	20–32	Decreased appetite/desire to eat	None (unknown effect duration)
Gluck and colleagues[147]	tDCS	L dlPFC	2 mA, anodal	3 40-min sessions over 3 days	9	42 ± 8	Decreased caloric consumption and greater weight loss compared to cathodal tDCS	None (unknown effect duration)
Bravo and colleagues[148]	tDCS	R dlPFC	2 mA, anodal	5 30-min sessions over 5 days	11	47 ± 11	Decreased food cravings but no weight loss	30 days (effect observed at last follow up)
Luzi and colleagues[153]	rTMS	Bl dlPFC	18 Hz	3 sessions per week for 5 weeks	11	–	Reduction in food cravings and weight loss	9 weeks (effect observed at last follow up)
Burgess and colleagues[149]	tDCS	Bl dlPFC	2 mA, anodal (R dlPFC), cathodal (L dlPFC)	Single 20-min session	30**	–	Decreased food cravings and food intake; decreased binge-eating desire in male participants only	None (unknown effect duration)
Ljubisavljevic and colleagues[150]	tDCS	R dlPFC	2 mA, anodal	5 40-min sessions over 5 days	13***	21 ± 2	Decreased food cravings	30 days (effect observed at last follow up)
Ray and colleagues[152]	tDCS	Bl dlPFC	2 mA, anodal (R dlPFC), cathodal (L dlPFC)	Single 20-min session	18	23 ± 8	No decrease in food cravings or intake overall; decreased cravings/consumption when trait scores were controlled	None (unknown effect duration)

Bl, bilateral; dlPFC, dorsolateral prefrontal cortex; L, left; rTMS, repetitive transcranial magnetic stimulation; R, right; tDCS, transcranial direct current stimulation.
*Only 11 of 19 participants were overweight or obese according to their BMI; **Burgess and colleagues' participants were both overweight (BMI > 24.5 kg/m^2) and met criteria for binge-eating disorder; ***Ljubisavljevic and colleagues also reported on 17 additional healthy participants with normal BMI.

compared to sham stimulation), limiting the interpretability of these results.[147] Bravo and colleagues further probed the applicability of NIBS for obesity by examining the effect of five sessions of right dlPFC tDCS (2 mA, 30 min) in a double-blind, sham-controlled manner within two cohorts of interest, one composed of 11 obese participants and the other comprising 10 Prader-Willi syndrome (PWS) patients. In both groups, active stimulation was associated with decreased food cravings (as well as reduced compulsive eating behaviors in the PWS cohort) but no weight loss at 30 days post-treatment.[148] Meanwhile, Burgess and colleagues conducted a blinded, sham-controlled trial of single-session dlPFC tDCS (2 mA, 20 min) in 30 overweight patients with binge-eating disorder using a right dlPFC anode/left dlPFC cathode montage.[149] During immediate post-treatment testing, active stimulation decreased both food cravings and food intake. Furthermore, it was reported to reduce binge-eating desire but not binge-eating frequency in male patients only. Another blinded, sham-controlled study demonstrated diminished cravings in 13 overweight/obese individuals that was maintained 30 days after five sessions of anodal right dlPFC tDCS (2 mA, 40 min), constituting the first description of sustained NIBS outcomes in this population.[150] It should be noted that the legitimacy of the blinding protocol has been questioned, however.[151] More recently, Ray and colleagues reported a double-blind sham-controlled trial of single-session bilateral dlPFC tDCS (2 mA, 20 min) in 18 obese participants employing the same right dlPFC anode/left dlPFC cathode montage described by Burgess and colleagues. Here, active stimulation failed to produce significant effects in the cohort overall but did reduce immediate post-treatment food cravings and food consumption in certain participant subgroups when trait scores (e.g. impulsiveness, intent to restrict calories) were controlled.[152]

Thus far, only a single study has looked at the effect of rTMS in obese participants. Luzi and colleagues found that 5 weeks of high-frequency (18 Hz) rTMS targeting bilateral dlPFC at a frequency of 3 sessions per week led to significant reductions in food cravings as well as weight loss in a cohort of 11 obese participants. Notably, this effect was maintained after 9 weeks and proved statistically significant in comparison to both inhibitory low-frequency rTMS and sham rTMS.[153]

NIBS for anorexia nervosa and bulimia nervosa

Thus far, five studies have investigated NIBS for AN (Table 4). Kamolz and colleagues first described a case report of left dlPFC rTMS in a patient with AN and comorbid depression (10 Hz, 2000 pulses, 41 sessions). According to this report, the patient's depressive symptomology was significantly improved and her BMI increased from 12.4 to 16 after 3 months (29% increase).[154] Two subsequent studies also yielded encouraging results with regard to AN and affective symptoms. Specifically, Van den Eynde and colleagues observed reduced perception of feeling fat, full and anxious in 10 AN patients immediately following left dlPFC rTMS (10 Hz, 1000 pulses, one session).[155] Meanwhile, Khedr and colleagues reported a trial of tDCS for AN, finding that 10 sessions of left dlPFC anodal stimulation (2 mA, 25 min) improved AN and depressive symptoms in five of seven patients immediately post-treatment and in three of seven patients at 1 month follow up.[156] More recently, McClelland and colleagues conducted a double-blind, sham-controlled trial examining the effects of a single session of left dlPFC rTMS (10 Hz, 1000 pulses) in 49 AN patients. This study demonstrated improved core AN symptoms and temporal discounting 24 h after treatment, lending support to earlier uncontrolled results.[157] A five-patient case series by the same group investigated the effect of high-frequency left dlPFC rTMS (10 Hz, 1000 pulses, 20 sessions) on both eating disorder and affective symptoms over 12 months, finding eating disorder symptoms to be improved in three of five patients and affective symptoms to be improved in two of five. Despite this, all five patients lost weight over the follow-up period, indicating that NIBS's impact on self-reported symptoms may not always translate to weight gain.[158]

NIBS has also been studied in BN. Thus far, two case reports, one case series and three randomized control trials have studied the effects of PFC rTMS for this indication (Table 5).[155,159–164] In both case studies, patients with comorbid BN and depression were treated with multiple sessions of rTMS and subsequently demonstrated improvement in depressive symptoms along with complete recovery from binging and purging symptoms in the short term. These results were observed immediately following 10 days of left dlPFC rTMS (20 Hz),[159] and up to 2 months after 20 days of bilateral dorsomedial PFC rTMS

Table 4. NIBS (rTMS and tDCS) for AN patients. This table illustrates seven cases of tDCS and 65 cases of rTMS DBS for AN.

Study	Modality	Indication	Target	Stimulation parameters	Stimulation timing	Number of patients	Age	Outcome	Follow up (effect duration)	Comorbidities
Kamolz and colleagues[154]	rTMS	AN	L dlPFC	10 Hz, 2000 pulses	41 sessions	1	24	BMI increase from 12.4 to 16 (29%)	3 months (effect observed at last follow up)	Depression
Van den Eynde and colleagues[155]	rTMS	AN	L dlPFC	10 Hz, 1000 pulses	Single session	10	18–44	Reduced perception of feeling fat, full, anxious	None (unknown effect duration)	Not specified
Khedr and colleagues[156]	tDCS	AN	L dlPFC	2 mA, anodal	10 25-min sessions over 10 days	7	16–39	Improved AN and depression symptoms in 5 patients immediately post-treatment, in 3 patients at 1 month post-treatment	1 month (effect observed at last follow up)	Depression, anxiety
McClelland and colleagues[158]	rTMS	AN	L dlPFC	10 Hz, 1000 pulses	20 20-min sessions	5	23–52	Improved eating disorder, affective symptoms; weight loss in all participants	12 months (effect observed at last follow up)	Not specified
McClelland and colleagues[157]	rTMS	AN	L dlPFC	10 Hz, 1000 pulses	Single 20-min session	49	~26±7.5	Improved AN core symptoms and temporal discounting	24 h (effect observed at last follow up)	Depression, anxiety

AN, anorexia nervosa; Bl, bilateral; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; L, left; rTMS, repetitive transcranial magnetic stimulation; R, right; tDCS, transcranial direct current stimulation.

Table 5. NIBS (rTMS and tDCS) for BN patients. This table illustrates 39 cases of tDCS and 122 cases of rTMS DBS for BN.

Study	Modality	Indication	Target	Stimulation parameters	Stimulation timing	Number of patients	Age	Outcome	Follow up (effect duration)	Comorbidities
Hausmann and colleagues[159]	rTMS	BN	L dlPFC	20 Hz	10 sessions over 10 days	1	28	Complete recovery from binging/purging episodes; ~50% depression improvement	None (unknown effect duration)	Depresion
Walpoth and colleagues[161]	rTMS	BN	L dlPFC	20 Hz, 2000 pulses	15 sessions over 15 days	14	~25 ± 7	No significant improvement in binge symptoms between sham and real rTMS	None (unknown effect duration)	Depression
Van den Eynde and colleagues[163]	rTMS	BN	L dlPFC	10 Hz, 1000 pulses	Single 20-min session	38	~30.5 ± 11	Decreased urge to eat, fewer binge-eating episodes	24 h (effect observed at last follow up)	–
Van den Eynde and colleagues[162]	rTMS	BN	L dlPFC	10 Hz, 1000 pulses	Single 20-min session	21 (7 left-handed)	~25 ± 13	Decreased craving; worsened mood in left-handed patients but improved mood in right-handed patients	None (unknown effect duration)	–
Downar and colleagues[164]	rTMS	BN	Bl dmPFC	10 Hz, 3000 pulses (per hemisphere)	20 sessions over 20 days	1	43	Full remission from binging/purging episodes, depression	2 months (effect observed at last follow up)	Depression
Gay and colleagues[160]	rTMS	BN	L dlPFC	10 Hz, 1000 pulses	10 20-min sessions over 10 days	47	19–40	No significant improvement in binging/purging symptoms between sham and real rTMS	15 days (effect observed at last follow up)	Depression, anxiety, alcohol/substance dependence
Kekic and colleagues[165]	tDCS	BN	L and R dlPFC (separate sessions)	2 mA, anodal	20 min sessions	39	18–48	Decreased urge to binge-eat, improved temporal discounting with both L and R dlPFC anodal tDCS; improved mood only following R dlPFC anodal tDCS	24 h (effect observed at last follow up)	Depression, anxiety

Bl, bilateral; BN, bulimia nervosa; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; L, left; mA, milliamps; rTMS, repetitive transcranial magnetic stimulation; R, right; tDCS, transcranial direct current stimulation.

(10 Hz, 3000 pulses).[164] Another case series compared the effect of single-session left dlPFC rTMS (10 Hz, 1000 pulses) on 14 right-handed patients and 7 left-handed patients, finding that the two groups exhibited decreased cravings immediately post-treatment but had opposing mood changes (improved mood in right-handed patients, worsened mood in left-handed patients).[162] However, results from randomized sham-controlled trials have been mixed. Van den Eynde and colleagues reported favorable results in their 38-patient trial of single-session left dlPFC rTMS (10 Hz, 1000 pulses), observing a significantly decreased urge to eat and fewer binge-eating episodes at 24 h post-treatment following stimulation compared to sham stimulation.[163] By contrast, an earlier study subjected a 14-patient cohort to 15 days of left dlPFC rTMS (20 Hz, 2000 pulses), but did not find any significant difference in binge symptoms between active and sham rTMS.[161] A similarly null result was obtained in a more recent 47-patient trial by Gay and colleagues, who found no difference in the rates of binging or purging symptoms over 15 days following a 10-day course of left dlPFC rTMS (10 Hz, 1000 pulses, 20 min).[160] The impact of tDCS on BN has been examined only once, in a randomized double-blind, sham-controlled trial in 39 patients. Interestingly, Kekic and colleagues found that both right and left dlPFC anodal tDCS (2 mA, 20 min) were associated with a decreased urge to binge-eat and improved temporal discounting 24 h post-treatment, but only right dlPFC was followed by improved mood.[165]

Conclusion

Obesity and eating disorders remain a significant burden on individuals and society. They are complex conditions that are difficult to treat given the underlying interplay between body homeostasis, reward pathways and affective/limbic circuitry. Despite aggressive medical and surgical management, there remain many refractory patients.

DBS offers a unique, long-lasting, modifiable and targeted treatment for obesity and eating disorders. Its applicability to these conditions is supported by both preclinical and clinical work. However, a number of further studies – including randomized controlled trials – are necessary to better determine DBS's effectiveness in this field. Furthermore, the exact stimulation parameters, anatomical targets, patient selection, timing and indications for DBS procedures need to be refined. While no significant side effects from any of the DBS targets has been noted to date, future trials should continue to include screening for depression, anxiety and changes in cognition in these weight- and affective-related disorders. In addition, it is worth noting that AN and morbidly obese patients are at increased risk of DBS complications such as infection and hardware erosion due to their poor nutritional status,[166] necessitating special surgical care in treating them.

NIBS has also shown promise for the treatment of obesity, anorexia and bulimia. A small number of randomized, sham-controlled trials have already explored the impact of NIBS for these indications, but further work is necessary to clarify equivocal results, delineate the long-term effects of treatment and better capture weight change-related outcomes in addition to cognitive and affective symptoms. NIBS represents a potentially important treatment option for obesity and eating disorders, given its excellent safety–feasibility profile and lack of serious side effects. However, key limitations of NIBS should be noted, including the need for continued recurrent dosing in order to avoid the wearing off of beneficial effects, the variability of targeting methods and uncertainty over the ideal stimulation parameters, and the variability of effects of different NIBS modalities in terms of their effect on target tissue.[151] Additional studies must address these shortcomings if NIBS is to become a reliable and effective tool for obesity and eating disorders. Taken together, these findings suggest a potential role for both DBS and NIBS in the treatment of morbid obesity and eating disorders.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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