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Title: Neuromodulation and Neurofeedback Treatments in Eating Disorders and Obesity

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Conflicts of interest

The authors have no conflicts of interest.

Key points

- During the last 20 months, several case studies/series and randomised controlled trials of non-invasive brain stimulation, deep brain stimulation, and neurofeedback in different eating disorders, obesity or food craving have appeared, with largely promising results.
- Ongoing trials in eating disorders and obesity will increase the evidence base for neuromodulation and neurofeedback procedures and help establish the validity of treatment protocols.
- Combining neuroimaging and neuromodulation techniques may help to identify distinct neural endophenotypes associated with differential intervention responses and may shed light on illness mechanisms.
- Much still needs to be learnt about patient selection, intervention parameters, treatment targets and how to optimise protocols.

Abstract

Purpose of review: Psychological interventions are the treatment of choice for most eating disorders (EDs), however, significant proportions of patients do not recover with these. Advances in understanding of the neurobiology of EDs have led to the development of targeted treatments, such as deep brain stimulation (DBS), non-invasive neuromodulation (NIBS) and neurofeedback. We review the emerging clinical evidence for the use of these interventions in EDs and obesity, together with their theoretical rationale. Finally, we reflect on future developments.

Recent findings: During the last 20 months, seven case studies/series and seven randomised controlled trials (RCTs) of NIBS or neurofeedback in different EDs, obesity or food craving have appeared. These have largely had promising results. One NIBS trial, using a multi-session protocol, was negative. A case series of sub-callosal DBS in anorexia nervosa has also shown promise. A search of trial registries identified a further 21 neuromodulation/feedback studies in progress, indicating that this is an area of growing interest.

Summary: At present neuromodulation and neurofeedback are largely experimental interventions; however, growing understanding of the mechanisms involved, together with the rising number of studies in this area means that the clinical utility of these interventions is likely to become clearer soon.

Key words: eating disorders, obesity, neuromodulation, neurofeedback

Introduction

Neuromodulation has been defined as use of “*advanced medical device technologies to enhance or suppress activity of the nervous system for the treatment of disease. These technologies include implantable as well as non-implantable devices that deliver electrical, chemical or other agents to reversibly modify brain and nerve cell activity*” [1]. These therapies are reversible and highly targeted to specific areas of the brain or spinal cord.

Improved understanding of the neurocircuitry involved in eating disorders (EDs) and obesity [e.g. 2, 3, **4] has given rise to the use of neuromodulation and neurofeedback as illness probes and as emerging treatments [5]. In particular, researchers have implicated alterations in circuits involved in reward processing [6-9], affect, stress and negative valence [10, 11], appetite regulation [12, 13], and self-regulatory control [6, 9]. To explain the extremes of behaviour across the spectrum of EDs (from severe food restriction/under-eating to overeating/binge eating), it has been proposed that these may result from a differentially altered balance between neural mechanisms of reward and inhibitory processing [9]. Neurobiological overlaps between EDs, obesity and addictions are being proposed [e.g. 14, 15, 16].

This review will focus on the most promising neuromodulation techniques, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and neurofeedback [3, 17, 18]. We will describe these techniques and stimulation targets, describe potential underlying mechanisms and summarise recent findings in relation to the application of these techniques to clinical and sub-clinical eating and weight disorders and their impact on ED and other outcomes. Finally, we will consider acceptability, tolerability, safety and ethical considerations.

Promising Neuromodulation Techniques and their Targets in Eating Disorders and Obesity

Deep brain stimulation (DBS)

This is a reversible neurosurgical intervention, whereby electrodes are implanted into a defined brain region and a battery-operated pulse generator (usually implanted in the chest) sends electrical pulses to the region to alter neural activity. Once implanted, the DBS device can be activated and programmed wirelessly, permitting real-time titration of stimulation parameters. Case studies of DBS to improve anorexia nervosa or comorbid symptoms (obsessive compulsive disorder, depression), targeting the nucleus accumbens, sub-genual cingulate cortex, ventral capsule/ventral striatum, or sub-callosal cingulate, have shown promise in highly selected severe and enduring cases [for review see 3, 18]. As yet, no RCTs have been carried out. Likewise in cases of severe obesity, hypothalamic or nucleus accumbens DBS has shown promise [for review see *19].

Non-invasive brain stimulation (NIBS)

In transcranial magnetic stimulation (TMS) an electrical current is passed through a TMS coil, thus

generating a magnetic field. When the coil is held against the head, the field induces a secondary electrical current (i.e. activation of neurons) in the targeted brain region. Repetitive transcranial magnetic stimulation (rTMS) involves the delivery of multiple pulses over a short time period with effects that outlast the stimulation period (30–60 min). Low frequency rTMS (<5 Hz) is thought to suppress neural activity, but high frequency rTMS (>5 Hz) is thought to enhance activity [20].

Transcranial direct current stimulation (tDCS) is a non-invasive form of brain stimulation. It involves the application of a low-intensity constant current (1–2mA) directly to the brain via scalp electrodes, which is thought to alter the electrical potential of neuronal membranes. Anodal (+ terminal) stimulation generally has cortical excitatory effects, whereas cathodal (– terminal) stimulation inhibits activity. Effects on cortical excitability can last beyond the stimulation period — up to 90 minutes. Long-term effects seem to operate through modifications of post-synaptic nerve connections, similar to long-term potentiation and long-term depression [20].

Candidate targets for NIBS in EDs, based on a ‘Research Domain Criteria (RDoC) formulation’ of ED pathology have been described [**4]. These include targets in the cognitive control, positive and negative valences, and social processes systems. For pragmatic accessibility reasons, studies have targeted the dorso-lateral prefrontal cortex (DLPFC) or the dorso-medial prefrontal cortex (DMPFC) [**4, 21]. Several case studies, case series, and proof-of-concept RCTs of NIBS have shown promise in EDs, obesity and food craving [22-26].

Neurofeedback

This form of biofeedback trains individuals to voluntarily regulate their brain activity in a target area in response to real time feedback [27]. The level of neural activity, as assessed via electroencephalography (EEG) or functional neuroimaging (fMRI), is fed back to the individual using a brain-computer interface and this provides continuously updated information about their success in regulating their neural activity [2, 17].

Evidence Supporting Different Types of Neuromodulation and Neurofeedback in Eating Disorders and Obesity

To provide an overview of recent clinical studies of invasive and non-invasive neuromodulation and neurofeedback in EDs and obesity, we systematically searched PubMed, Scopus, and Web of Science, using the following search terms: brain stimulation OR “TMS” OR transcranial magnetic stimulation OR “tDCS” OR “transcranial direct current stimulation” OR transcranial stimulation OR neurofeedback combined with food OR eating OR body OR anorexia OR anorexi* OR bulimia OR bulimi* OR obesity OR obes* OR binge eat*. We limited our search to articles in English published between October 2015 and May 2017. We excluded studies where the focus was not on changes to eating behaviours or body

weight as a result of neuromodulation/neurofeedback (see Tables 1-3).

To provide an overview of forthcoming but unpublished studies, we searched major national and international clinical trials registries, including the World Health Organization's International Clinical Trials Registry, clinicaltrials.gov, ISRCTN registry, the Australian and New Zealand Clinical Trials Registry, ANZCTR, (using the above search terms individually). Details of these studies are presented in Table 4.

DBS

Our search identified one single case study of DBS in anorexia nervosa [28] and one open label trial of DBS, targeting the subcallosal cingulate cortex in 16 patients with chronic treatment-refractory anorexia nervosa [*29] (see Table 1). This was an extension of an earlier series of 6 patients [65] and is the largest series of DBS for anorexia nervosa. DBS treatment was associated with significant and sustained improvements in anxiety, depression and emotion regulation, and significant increases in body-mass index (BMI) at 12 months post-surgery [*29]. PET imaging showed significant changes in glucose metabolism in brain structures implicated in anorexia nervosa at 6 and 12 months follow-ups, compared with baseline, suggesting that DBS can directly affect anorexia-related brain circuitry. Two patients asked to have their device removed for poorly explained reasons. Ten out of 16 patients experienced at least one adverse event, however only one was thought to be DBS related (surgical site infection), most others were related to the underlying illness. A single case study of nucleus accumbens DBS in obesity was also identified [30].

NIBS

We identified 8 NIBS studies (n=232 participants), all targeting the DLPFC (see Table 2)

Anorexia nervosa:

Two studies assessed use of rTMS in anorexia nervosa. In a sham-controlled RCT, a single session of real rTMS, led to greater short-term reduction in ED symptoms and improved reward-related decision-making (assessed through a temporal discounting paradigm) [*31]. In a subsequent case series, five adults with severe and enduring anorexia nervosa received 20 sessions of real rTMS [32]. This was associated with reductions in ED and affective symptoms. Improvements persisted up to 6 months post-treatment but had waned by 12 months.

Bulimia nervosa:

Recent NIBS studies have shown mixed results in bulimia nervosa. A case series of single-session high-frequency rTMS found reductions in food craving and hunger, but no change in ED symptoms [33].

Likewise, a sham-controlled RCT of ten sessions of high-frequency rTMS in bulimia nervosa participants found no difference between groups in ED symptoms post-treatment [*34]. However, the study was limited, in that the stimulation target was not localised by neuronavigation and the number of rTMS sessions was relatively low.

In contrast, a cross-over RCT using tDCS in bulimia nervosa, found that one session of anode right/cathode left active tDCS (but not anode left/cathode right active or sham tDCS) lead to improvements in cognitions and mood at post-treatment [*35]. Both active tDCS conditions suppressed the self-reported urge to binge-eat and increased self-regulatory control (assessed through temporal discounting paradigm). Group differences in frequency of ED symptoms were not observed 24-hours post-tDCS.

Food craving, Binge Eating Disorder and Obesity:

A study of healthy individuals with high food cravings, found active tDCS applied over 5 consecutive days significantly reduced food cravings in comparison to sham tDCS, both post-treatment and one month later [36].

In a cross-over study, participants with binge eating disorder experienced reduced cravings for certain foods and consumed fewer calories following a single session of active tDCS, compared to sham tDCS [*37].

Participants with obesity consumed fewer kilocalories/day from fat and soda and had a greater percentage weight loss, during active anodal tDCS treatment to the left DLPFC, compared to during cathodal tDCS [38]. There was no difference between sham and active groups in relation to weight change or food intake.

Neurofeedback

EEG neurofeedback has been investigated in two RCTs (see Table 3). Significant training effects were shown in eating behaviour, emotion regulation, and in some EEG parameters (although not as hypothesised) in a trial of EEG neurofeedback in adolescents with anorexia nervosa [*39]. Secondly, in participants with subthreshold binge eating disorder, 10 sessions of EEG neurofeedback (but not mental imagery and waitlist) reduced the frequency of binge eating post-treatment and at 3-months follow-up [*40].

Real-time fMRI neurofeedback has been assessed in one case series in individuals with obesity [*41]. In this proof-of-principle study, participants successfully managed to increase functional connectivity between the DLPFC and VMPFC, areas of the brain associated with executive control and reward

processing. Despite this, there was only a trend effect of neurofeedback training on food choice towards less high-calorie foods.

Ongoing studies of neuromodulation and neurofeedback

Details of 21 ongoing studies are presented in Table 4. The majority are trials of NIBS, with roughly equal numbers of rTMS and tDCS protocols. For both modalities, the majority of studies involve multiple sessions, targeting the prefrontal cortex. Additionally, there are five DBS studies in progress, three in anorexia nervosa and two in obesity. These trials will increase the evidence base for these procedures and help establish the validity of treatment protocols.

An Emerging Scientific Rationale for the Use of Neuromodulation/ Neurofeedback

It is beyond the scope of this paper to discuss extensively the evidence relating to different putative mechanisms of action underpinning different neuromodulation treatments. The interested reader may wish to consult the following reviews [e.g. 20, 66, 67]. Here, we briefly focus on two promising areas of investigation, the combination of neuroimaging and neuromodulation data, and secondly, the role of mechanisms related to memory reconsolidation.

Neural correlates and predictors of change

Studies combining neuroimaging and neuromodulation data are in their infancy in EDs. Such studies might be able to identify distinct neural endophenotypes, associated with differential intervention responses at the neural and the clinical level; they might also help tailor rTMS parameters to individual patients and they may shed light on illness mechanisms and strengthen the scientific rationale for the use of neuromodulation [68]. The first functional neuroimaging study in EDs patients undergoing NIBS involved 28 patients with longstanding binge-purge behaviours and failed previous treatments [68]. All received 20-30 sessions of 10 Hz DMPFC-rTMS. Based on a criterion of $\geq 50\%$ reduction in weekly binge/purge frequency, participants were stratified into 16 treatment responders and 12 non-responders. There were widespread differences between the two groups in resting-state neural connectivity at baseline. Relative to non-responders, rTMS-responders showed baseline hypo-connectivity from the stimulation target to other cortical and subcortical regions. In responders, fronto-striatal connectivity was enhanced following DMPFC-rTMS, in association with reductions in binge-purge frequency. Conversely, in patients with higher baseline connectivity, DMPFC-rTMS had the opposite effect, reducing fronto-striatal connectivity, in association with worsening of or failure to improve symptoms. The need to conceptualise change in terms of neural networks in relation to neuromodulation in psychiatric disorders has been reviewed [**69].

The role of learning and memory reconsolidation

As described, many studies emphasise the importance of motivational salience, reward and learned behaviours, and are consistent with neuromodulation that targets frontostriatal circuits. However, it is important to recognize the emerging role of learning in the development/maintenance of psychiatric illnesses, such as EDs, and the role of new learning in treatment [70, 71]. For this reason, it is appropriate to consider the neural underpinnings of memory as a potential neuromodulation target. Of particular clinical interest is reconsolidation, the process by which memories can be made labile via reactivation [e.g. 72, 73]. Reconsolidation is increasingly being used as a treatment target based on the assumption that psychological treatments are most effective when links between illness-relevant stimuli and maladaptive emotional, cognitive or behavioural responses are broken [e.g. 70]. This is the objective of exposure treatments [74, 75], however, an alternative approach is to update emotional memories by changing their salience during reconsolidation [76], using psychological or [e.g. 77, 78, 79] pharmacological approaches [e.g. 80, 81-83]. Importantly, neuromodulation reportedly alters memory reconsolidation, and some studies have begun to assess the effects of tDCS on reconsolidation [84]. Mechanisms centre around the proposal that new memories arise when the balance between excitatory (glutamatergic) and inhibitory (GABA-ergic) (E-I) firing patterns are disrupted [61, 62], as can be promoted by neuromodulation. For example, tDCS has been shown to decrease GABA concentrations and hence may modulate the relationship between glutamate and GABAergic systems [61]. On the basis of such studies, our opinion is that molecular/physiological studies related to neuromodulation will need to identify which neurotransmitter systems are the main targets e.g. 5-HT (in relation to affect regulation), DA (in relation to reward and habits) and/or glutamate/GABA (E-I) (in relation to memory and synaptic plasticity). The importance of E-I systems in psychopathology and across psychiatric phenotypes has recently been discussed [e.g. 86] but, if explanatory models of neuromodulation increasingly centre around E-I systems, neuromodulation might be most effective as an adjunct to treatments involving memory reconsolidation. Lastly, the E-I balance and its relation to synaptic plasticity is an evolving subject and the complexity involved is likely to increase.

Acceptability, Safety and Ethical Considerations

In general, safety and acceptability of NIBS do not appear to be a problem [e.g. 87, 88, 89]. For example, a systematic review of tDCS studies found similarly low drop-out rates for real and sham tDCS [88]. However, these authors noted that the quality of adverse events reporting was low in most studies. Very limited research on this issue has been conducted in relation to EDs [90].

Ethical considerations have mainly focused on DBS rather than on NIBS, given the invasiveness of DBS and its use in highly vulnerable, physically frail anorexia nervosa patients, whose capacity for making health-related decisions may be impaired. Additionally, families desperate to alleviate their loved one's distress may push them towards agreeing to DBS. Other concerns have included the issue that DBS or NIBS might be perceived as '*mind control*', increasing patients' helplessness and reducing

their sense of authenticity [91, 92]. The limited literature exploring ED patients' views shows that they are able to understand and reflect on issues related to gains and threats to their authenticity [93, 94]. In a case series (n=5) of therapeutic rTMS in anorexia nervosa, patients were asked about their experience [32]. They talked about greater cognitive clarity, flexibility and improved mood. There was no sense of altered authenticity or agency. Recently a neuro-ethics framework for the use of DBS in anorexia nervosa has been published [**95].

Discussion

During the last 20 months, seven case studies/series and seven RCTs of NIBS or neurofeedback in different EDs, obesity or food craving have appeared, with largely promising results. However, one NIBS trial, using a multi-session protocol in bulimia nervosa, was negative. A case series of sub-callosal DBS in anorexia nervosa has also shown promise. A search of trial registries identified a further 21 ED-focused neuromodulation/feedback studies in progress, suggesting that this is an area of growing interest. In parallel, safety, acceptability and ethical considerations are being systematically studied. Progress is also being made in relation to developing a rationale for use of neuromodulation treatments, substantially based on neural models of EDs/obesity, including the role of memory and its reconsolidation in their development and treatment. These advances together with the rapidly increasing knowledge of neural networks and their interconnectivity will lead to the formulation of new hypotheses on the aetiology and treatment of EDs.

Whilst the evidence suggests that neuromodulation treatments have potential, as probes of illness mechanisms and as potential interventions in the treatment of EDs and obesity, much of this potential is still waiting to emerge. Much needs to be learnt about patient selection, intervention parameters, treatment targets and how to optimise protocols. Neurocognitive, neural and genetic predictors of outcome may help to individualise protocols and deliver personalised treatment.

At present, the rationale for use of one NIBS procedure over another is unclear. Ultimately this may be mostly influenced by practical considerations such as costs, availability and commercial interests. In this respect, it is noted that portable tDCS devices are available, which can be used at home.

Neuromodulation technologies continue to evolve, and for example, in the case of NIBS, are increasingly allowing more precise targeting of treatment, use of increasingly briefer and more powerful treatment protocols, probing deeper brain areas and stimulating multiple brain targets simultaneously [**4]. There is emerging evidence suggesting that these kinds of interventions may work synergistically when applied with different forms of cognitive training, as yet this combination treatment is unexplored in EDs. A framework for combining rTMS with behavioural interventions has been described [96]. Finally, another promising neurotechnology is fMRI neurofeedback, which as yet has not been explored

in relation to anorexia nervosa [17].

Conclusion

At present neuromodulation and neurofeedback are largely experimental interventions; however, growing understanding of the mechanisms involved, together with the rising number of studies in this area means that the clinical utility of these interventions is likely to become clearer soon.

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Table 1. Recent research studies of deep brain stimulation in weight and eating disorders.

Author	<i>N</i>	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Anorexia Nervosa								
Blomstedt et al. (2017) [28]	1	Adult female with chronic AN and severe MDD	DBS	Case study	Bed nucleus of the stria terminalis (BNST)	Bilateral stimulation of 130 Hz, 120 μ s pulse width, and 4.3V (at 12 months post-surgery) to the BNST	Food and eating-related anxiety and obsessive thoughts vanished. Virtually stopped vomiting. Food intake more stable and less prone to large variations. No effect on BMI. Profound improvement in depression nine months post-surgery.	Electrodes initially implanted in MFB, but due to side effects, stimulation was turned off. Re-operated on for DBS of the BNST two years after first operation.
Lipsman et al. (2017) [*29]	16	Adults with enduring AN	DBS	Open-label trial	Subcallosal cingulate	Bilateral stimulation of 130 Hz, 90 μ s pulse width and 5-6.5 V (at 12 months post-surgery) to the subcallosal cingulate	Mean BMI increased significantly and, anxiety, depression and affective regulation improved over the 12 months post-surgery.	
Obesity								
Harat et al. (2016) [30]	1	Adult female with hypothalamic obesity	DBS	Case study	Nucleus accumbens	Bilateral stimulation of 208 μ s pulse width, 130 Hz, and 3.75mA (final value) to the nucleus accumbens	BMI decreased from 52.9 pre-surgery to 48.3 14 months post-surgery, which was accompanied by improvement in the emotional state.	

N = number of participants; DSM = Diagnostic and Statistical Manual of Mental Disorders; AN = anorexia nervosa; MDD = major depressive disorder; DBS = deep brain stimulation; Hz = hertz; μ s = microsecond; V = volts; BMI = body mass index; MFB = medial forebrain bundle

Table 2. Recent research studies of NIBS in weight and eating disorders.

Author	<i>N</i>	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Anorexia Nervosa								
McClelland et al. (2016) [*31]	60	Adults with DSM-5 AN Right handed	rTMS	RCT Double-blind parallel group Conditions: (i) Real rTMS (ii) Sham rTMS	Left DLPFC Neuronavigation	20 × 5 s trains/55 s inter-train interval at 10 Hz = 1000 pulses per session; 110% MT 1 session	In completers (n=49), core AN symptoms were significantly reduced post-rTMS and at 24-hour follow-up in the real, but not sham, rTMS group.	Proof-of-concept trial
McClelland et al. (2016) [32]	5	Females with chronic treatment-refractory DSM-5 AN Right handed	rTMS	Case series	Left DLPFC Neuronavigation	20 × 5 s trains/55 s inter-train interval at 10 Hz = 1000 pulses per session; 110% MT ~20 sessions	From pre- to post-treatment, ED and affective symptoms improved significantly and further improvements were seen at 6 months post-treatment.	
Bulimia Nervosa								
Sutoh et al. (2016) [33]	8	Adults with DSM-IV-TR BN Right handed	rTMS	Case series	Left DLPFC Located using 5 cm anterior method	20 × 5 s trains/55 s inter-train interval at 10 Hz = 1000 pulses per session; 110% MT 1 session	At 4-hours post-rTMS, a significant reduction in the subjective ratings of want to eat, urge to eat, and sense of hunger for high-calorie food stimuli was found. No effect on eating disorder symptoms was identified.	

Gay et al. (2016) [*34]	51	Females with DSM-IV BN Right handed	rTMS	RCT Double-blind parallel group Conditions: (i) Real rTMS (ii) Sham rTMS	Left DLPFC Located using 6 cm anterior method	20 × 5 s trains/55 s inter-train interval at 10 Hz = 1000 pulses per session; 110% MT 10 sessions	At post-treatment, no group differences in number of binges in 15 days post-treatment, features of binge episodes, number of days without bingeing, maximal craving before a binge, number of vomiting episodes and mood.	
Kekic et al. (2017) [*35]	39	Adults with DSM-5 BN Right handed	tDCS	RCT Double-blind sham-controlled crossover Conditions: (i) Active tDCS: anode left / cathode right (ii) Active tDCS: anode right / cathode left (iii) Sham tDCS	DLPFC Located using 10–20 EEG system (F3 for left DLPFC and F4 for right DLPFC)	2 mA; 20 minutes 1 session per condition	Anode right / cathode left active tDCS led to reductions in eating disorder cognitions and improvement in mood, compared to the other active and sham condition. Both active conditions suppressed the self-reported urge to binge-eat.	
Frequent Food Cravings, Binge Eating Disorder, and Obesity								
Ljubisavljevic et al. (2016) [36]	30	Healthy adults with high food cravings Right handed	tDCS	RCT Conditions: (i) Active tDCS: anode right/cathode left forehead (ii) Sham tDCS	Right DLPFC Located using 10–20 EEG system (F4 for right DLPFC)	2 mA; 20 minutes 5 sessions; 1 per day for 5 days	Food cravings were significantly reduced by the end of treatment and at 30 days post-treatment in the active, but not the sham, group.	Sham group: Received real stimulation on 1 st session

Burgess et al. (2016) [*37]	30	Adults with full or subthreshold (n=11) BED	tDCS	Single-blind sham-controlled crossover Conditions: (i) Active tDCS: anode right / cathode left (ii) Sham tDCS	DLPFC Located using 10–20 EEG system (F3 for left DLPFC and F4 for right DLPFC)	2 mA; 20 minutes 1 session per condition	Active tDCS decreased craving more than sham for desserts, savoury proteins, and the all-foods category. Participants ate less total kcals in the lab after active tDCS compared to following sham tDCS.	Active tDCS reduced desire to binge-eat 5-6 hours post-tDCS, but only in male participants.
Gluck et al. (2015) [38]	9	Adults with obesity	tDCS	Double-blind, randomized, placebo-controlled crossover Conditions: (i) Active tDCS: cathode left / anode left forearm (ii) Active tDCS: anode left / cathode above right eye (iii) Sham tDCS	Left DLPFC Located using 10–20 EEG system (F3 for left DLPFC)	2mA; 40 minutes 3 sessions; 1 per day for 3 days	Participants consumed significantly fewer kilocalories from soda and fat, and had a greater percentage weight loss during anodal compared to cathodal tDCS. No difference between sham and active groups for weight change or any food intake measure.	All participants received 2 treatment courses, maintaining original assignment to active and sham i.e. active group received both active tDCS montages, sham group received sham stimulation twice.

N = number of participants; tDCS = transcranial direct current stimulation; rTMS = repetitive transcranial magnetic stimulation; EEG = electroencephalogram; DSM = Diagnostic and Statistical Manual of Mental Disorders; RCT = randomized controlled trial; mA = milliamps; Hz = hertz; MT = motor threshold; s = seconds; AN = anorexia nervosa; BN = bulimia nervosa; BED = binge eating disorder; imaging; dlPFC = dorsolateral prefrontal cortex

Table 3. Recent research studies of neurofeedback weight and eating disorders.

Author	N	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Anorexia Nervosa								
Lackner et al. (2016) [*39]	22	Female adolescents with DSM-5 AN	EEG Neurofeedback	RCT Conditions: (i) Experimental: TAU plus Neurofeedback (EG) (ii) Control: TAU (CG)	N/A	Individual alpha frequency training 10 sessions, 2 per week for 5 weeks	At post-treatment, significant training effects were shown in eating behaviour, emotion regulation, and in some EEG parameters, although not as hypothesised.	Rationale: alpha neurofeedback is supposed to be stress reducing.
Binge Eating Disorder and Obesity								
Schmidt & Martin (2016) [*40]	75	Adults with subthreshold BED	EEG neurofeedback	RCT Conditions: (i) EEG neurofeedback (ii) Mental Imagery (iii) Waitlist	N/A	Neurofeedback following food exposure 10 sessions over 6 weeks	Only EEG neurofeedback led to a reduced frequency of binge eating. Distress associated with binge eating was reduced in both active conditions. The effects remained stable to a 3-month follow-up.	
Spetter et al. (2017) [*41]	8	Male adults with obesity	fMRI Neurofeedback	Case series	dIPFC and vmPFC	Real-time fMRI neurofeedback; training to up-regulate functional connectivity between the dIPFC and vmPFC	Participants successfully learned to increase functional connectivity between dIPFC and vmPFC. No significant effect of training on food choice.	

						6 sessions over 4 weeks		
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N = number of participants; DSM = Diagnostic and Statistical Manual of Mental Disorders; AN = anorexia nervosa; EEG = electroencephalogram; RCT = randomized controlled trial; TAU = treatment-as-usual; N/A = not applicable; BED = binge eating disorder; fMRI = functional magnetic resonance imaging; dlPFC = dorsolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex

Table 4. Ongoing research studies of neuromodulation and neurofeedback treatments in EDs and obesity.

Author(s), Year	N	Sample	Inclusion criteria	Design	Protocol	Primary Outcome
DBS						
Aziz & Park (2013) [42]	6	AN	Females with DSM-IV AN, aged 20-65, illness duration > 7 years, treatment refractoriness according to pre-specified criteria, BMI 13-16	Open label trial Safety/Efficacy Study	DBS of the nucleus accumbens / anterior limb of internal capsule	Adverse events associated with surgery or stimulation 13 month post-surgery, eating disorder pathology at 15 months assessed using the Eating Disorder Examination and the Yale Brown Eating Disorder Scale, BMI at 15 months
Gao (2015) [43]	10	AN	Adults with DSM-5 AN, age 18-65, BMI < 16, long-term pharmacotherapy resistance	Single blind randomized parallel	Continuous DBS of bilateral nucleus accumbens vs. Treatment with Fluoxetine	BMI at 6 months
Gorgulho et al. (2014) [44]	6	Obesity	Adults with obesity, aged 18-65, BMI > 40, failed diet, exercise, behaviour, and pharmacotherapy to control body weight	Open label, feasibility trial	DBS of the ventromedial hypothalamus	Identification of possible adverse events after 12 months
Luming & Fumin (2016) [45]	16	AN	Adults with DSM-5 AN-R or AN-BP, aged 20-60, chronicity or treatment resistance according to pre-specified criteria	Open label trial Safety/Efficacy Study	DBS; target not reported	Change from baseline in Eating Disorder Related Preoccupations and Rituals scores at 3 months, 6 months and 12 months post-surgery
Rezai (2012) [46]	3	Obesity	Adults with obesity, aged 22-60, at least 24-months post-gastric bypass surgery without evidence of a sustained	Feasibility study	DBS; target not reported	Percentage of excess weight loss after 2 years

			improvement in BMI after gastric bypass surgery for at least 6 months			
tDCS						
Choi (2015) [47]	15	Obesity	Adults with obesity, aged 20-80, BMI > 28	Double-blind crossover	1 session per condition 2 mA; 20 minutes Real tDCS vs. Sham Anode: Right DLPFC, Cathode: Left DLPFC	Regional brain activity measured by blood-oxygen-level dependent signal of functional MRI immediately after intervention
Guillaume (2016) [48]	10	AN	Females with DSM-5 AN, illness duration > 3 years, aged 18-50, failure of at least one outpatient treatment conducted by a specialized team, BMI > 13.5	Open label treatment trial Pilot study	20 sessions: twice a day for 2 weeks 2mA; 25 minutes Anode: Left DLPFC, Cathode: Right DLPFC	Eating Disorder Examination - Questionnaire score at baseline and 1 month after last session of tDCS
Mostafavi (2016) [49]	50	Obesity	Adults with overweight or obesity, aged 18-50, BMI > 25	Single blind randomized parallel	10 sessions 2 mA; 20 minutes Real tDCS vs. Sham, both followed by a weight loss diet Target not reported	Weight at baseline and after 2, 6, and 8 weeks
Piravej (2013) [50]	64	Obesity	Adults with overweight or obesity, aged 20-60, BMI > 25	Randomized sham-controlled trial	12 sessions: 3 sessions per week for 4 weeks 2 mA; 20 minutes Real tDCS vs. Sham	Visual analogue scales of "appetite" at baseline and 2 and 4 weeks after intervention

					Anode: Right DLPFC, Cathode: Left DLPFC	
Sandegani (2016) [51]	20	Food craving	Males with a food craving score at least one standard deviation higher than population mean, aged 18-70, BMI < 40	Single blind randomized parallel	1 session 2 mA; 20 minutes Real tDCS vs. Sham Anode: Right DLPFC, Cathode: Left DLPFC	Visual analogue scale of "food craving" at baseline, during and immediately after stimulation
Vicari et al. (2015) [52]	160	AN & BED	Adolescents aged 13 to 18, diagnosis of either DSM-5 AN (BMI below 5th percentile) or BED with BMI > 85th percentile	Double blind randomized parallel	18 sessions: 3 times a week over 6 weeks 1mA; 20 minutes Real tDCS vs. Sham AN: Anode: Left DLPFC, Cathode: Right DLPFC BED: Anode: Right DLPFC, Cathode: Left DLPFC	Proportion of patients in each treatment arm with change in > 1 point of the total score of the Eating Disorder Inventory-3 questionnaire at 6 weeks
rTMS						
Avinoach et al. (2016) [53]	60	Obesity	Adults with obesity, aged 22-70, BMI 30-40, have had at least one prior conventional weight loss attempt, but no current weight loss attempts	Single blind randomized parallel	Number of sessions not reported. High frequency real deep TMS - right-to-left DLPFC vs. High frequency real deep TMS - left-to-right DLPFC vs. Sham Target: DLPFC	Change in weight between baseline, end of treatment (day 15) and 1 month post-treatment
Bartholdy et al. (2015) [54, 55]	30	AN	Adults with DSM-5 AN-R or AN-BP, illness	Randomized sham-controlled	20 sessions: 5 days per week for 4 weeks	None defined as this is a feasibility trial.

			duration > 3 years, aged 18 or over, BMI 14-18.5, must have completed at least one adequate previous course of eating disorder treatment	trial Feasibility trial	High frequency real rTMS vs. Sham Target: Left DLPFC	
Chastan (2013) [56]	54	AN	Females with AN-R, aged 18-80, illness duration 1-3 years, BMI<16	Double blind randomized sham-controlled parallel	10 sessions: in 2 weeks High frequency real rTMS vs. Sham Target: Inferior parietal cortex	Body Shape Questionnaire (BSQ-34 scale) score immediately after rTMS
Claudino et al. (2015) [57, 58]	90	BED	Females with DSM-5 BED, aged 18-55, BMI > 35	Double blind randomized sham-controlled parallel	20 sessions: 3 sessions a week over approximately 7 weeks High frequency real rTMS vs. Sham Target: Left DLPFC	Change in number of weekly binge eating episodes and craving between baseline and 2 months
Downar & Woodside (2016) [59]	240	AN-BP or BN	Adults with AN-BP or BN, aged 18-65, outpatient, failed to achieve clinical response to at least one pharmacological or behavioural treatment in current episode	Randomized sham-controlled trial	30 sessions: twice daily, 5 days per week for 3 weeks High frequency real rTMS (20 Hz) vs. Low frequency real rTMS (1 Hz) vs. Sham Target: DMPFC	Weekly BP frequency on Eating Disorder Examination at baseline, after each week of treatment, and 2, 6, and 12 weeks post-treatment

Ferrulli & Luzi (2015) [60]	50	Obesity	Adults with obesity, aged 22-65, BMI 30-45	Double blind randomized sham-controlled parallel	15 sessions: 3 days per week for 5 weeks High frequency real deep TMS vs. Low frequency real deep TMS vs. Sham Target: PFC and insula	Changes in food craving levels measured by the Food Cravings Questionnaire-Trait from baseline to end of treatment, and at 1 month, 6 months and 12 months post-treatment
Kim (2015) [61]	60	Obesity	Adults with overweight or obesity, aged 19-65, BMI > 25	Double blind randomized sham-controlled parallel	4 sessions: 2 days per week High frequency real rTMS vs. Sham Target: Left DLPFC	Change in body weight 4-weeks post-treatment
Nakazato (2014) [62]	48	AN, BN & BED	Adults with DSM-5 AN, BN or BED, aged 20-49, treatment resistant according to pre-specified criteria	Randomized sham-controlled trial	Number of sessions not reported. High frequency real rTMS vs. Sham Target: Left DLPFC	Change in visual analogue scale of "urge to eat" (administered before and after the rTMS sessions)
Neurofeedback						
Hilbert & Blume (2016) [63]	60	BED	Adults with DSM-5 BED with low frequency or low duration, aged 18-60, BMI 25-45	Randomized controlled trial	EEG Neurofeedback 10 sessions: over 6 weeks Arm 1: Neurofeedback of specific EEG frequencies to reduce high beta activity and increase theta activity on electrode positions Cz, Fz, Fc1, and Fc2. Arm 2: Neurofeedback of the slow cortical potentials on EEG electrode position Cz.	Number of binge-eating episodes at the end of treatment assessed using the Eating Disorder Examination

Perchik & Cina (2015) [64]	5	Obesity	Males with obesity, aged 20-50, BMI 28-35	Open label trial	Hematoencephalography (HER) bio/neurofeedback using a HER and Near Infra-Red sensor. Based on differential oxygenated blood supply according to regional brain activity.	Increase in brain activity in frontal brain areas after 7 weeks
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N = number of participants; tDCS = transcranial direct current stimulation; rTMS = repetitive transcranial magnetic stimulation; DBS = deep brain stimulation; EEG = electroencephalogram; DSM = Diagnostic and Statistical Manual of Mental Disorders; RCT = randomized controlled trial; mA = milliamps; Hz = hertz; MT = motor threshold; s = seconds; AN = anorexia nervosa; BN = bulimia nervosa; BED = binge eating disorder; imaging; dlPFC = dorsolateral prefrontal cortex; dmPFC= dorsomedial prefrontal cortex; PFC = prefrontal cortex; BMI = body mass index