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REVIEW ARTICLE

Neurostimulation in Clinical and Sub-clinical Eating Disorders: A Systematic Update of the Literature

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Abstract: ***Introduction*:** Whilst psychological therapies are the main approach to treatment of eating disorders (EDs), advances in aetiological research suggest the need for the development of more targeted, brain-focused treatments. A range of neurostimulation approaches, most prominently repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS), are rapidly emerging as potential novel interventions. We have previously reviewed these techniques as potential treatments of EDs.

***Aim*:** To provide an update of the literature examining the effects of DBS, rTMS and tDCS on eating behaviours, body weight and associated symptoms in people with EDs and relevant analogue populations.

***Methods*:** Using PRISMA guidelines, we reviewed articles in PubMed, Web of Science, and PsycINFO from 1st January 2013 until 14th August 2017, to update our earlier search. Studies assessing the effects of neurostimulation techniques on eating and weight-related outcomes in people with EDs and relevant analogue populations were included. Data from both searches were combined.

***Results*:** We included a total of 32 studies (526 participants); of these, 18 were newly identified by our update search. Whilst findings are somewhat mixed for bulimia nervosa, neurostimulation techniques have shown potential in the treatment of other EDs, in terms of reduction of ED and associated symptoms. Studies exploring cognitive, neural, and hormonal correlates of these techniques are also beginning to appear.

***Conclusions*:** Neurostimulation approaches show promise as treatments for EDs. As yet**,** large well-conducted randomised controlled trials are lacking. More information is needed about treatment targets, stimulation parameters and mechanisms of action.

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1. INTRODUCTION

In recent years, there has been a conceptual shift in psychiatry and clinical psychology, in that there is increasing acceptance that clinical approaches to mental health problems should not remain "brainless": in this respect, the eating disorders (EDs) are no exception [1]. This paradigm shift has crucially been influenced by developments in basic neuroscience that have increased our understanding of neural pathways and function, such as optogenetics [2], but arguably, the change is mainly due to the increasing clinical and experimental use (and sophistication) of structural and functional neuroimaging, *e.g*. magnetic resonance imaging (MRI) [3]. These studies have fostered the development of brain-based aetiological models of illness and there is the expectation that these will inform advances in treatment, leading to more targeted and personalised treatments. This applies across psychiatry and again EDs are no exception. In EDs, for many years, the majority of structural and functional neuroimaging studies have focussed on anorexia nervosa (AN) [4, 5-8] and to a lesser extent on bulimia nervosa (BN) [9]. However, there is increasing interest in binge eating disorder (BED) and in obesity [10, 11]. There is also interest in the development of spectral models that can accommodate a transdiagnostic framework for these problems [12, 13].

Many of the neural-based models of EDs are centred around an altered balance between neural mechanisms related to reward and those related to cognitive control/inhibitory systems [14, 15]. Importantly, and as discussed below, they have boosted the development and use of neurostimulation studies in EDs both as illness probes and as

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potential treatment modalities. They have also provided a rationale for treatment targets, such as the nucleus accumbens for deep brain stimulation (DBS) in AN and the dorsolateral prefrontal cortex (DLPFC) for the application of non-invasive neurostimulation procedures (such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS)). Conversely, as is described below, neurostimulation studies are gradually beginning to inform models of illness and treatment.

Neurostimulation has been defined as *'any intervention intended to alter nervous system function by using energy fields such as electricity, magnetism, or both'* [16]. Contemporary therapeutic neurostimulation methods use a range of implantable and non-implantable devices to reversibly enhance or suppress brain and neuronal activity for the treatment of disease. The most widely used neurostimulation method in psychiatry remains electro-convulsive therapy (ECT), but - given its side effect and safety profile - ECT is increasingly limited to life-threatening psychiatric disorders, such as severe depression or catatonia. More modern neurostimulation treatments include DBS, repetitive TMS (rTMS) and tDCS. These are the treatments that will be considered here.

Information on these neurostimulation techniques is summarised in Table **1**. As can be seen, DBS is a reversible neurosurgical intervention in which electrodes are implanted in a defined brain region, such as the nucleus accumbens, subgenual cingulate cortex, ventral capsule/ventral striatum (VC/VS), or subcallosal cingulate (SCC) and a battery-operated pulse generator (implanted in the chest) is used to alter neural activity. The device is programmed wirelessly, permitting titration of stimulation parameters. With TMS, an electrical current in a coil generates a magnetic field, which induces a secondary electrical current in the targeted brain region. rTMS involves multiple pulses over a short time period with effects that outlast the stimulation period (30–60 min). Low frequency rTMS is thought to suppress neural activity, and high frequency rTMS to enhance activity. rTMS can lead to lasting changes in brain function, *i.e*. there is some evidence that it leads to long term depression (LTD) and long term potentiation (LTP) in neural systems. tDCS is also non-invasive. It involves application of a low-intensity constant current (1–2mA) to the brain *via* scalp electrodes. Anodal stimulation generally has cortical excitatory effects, whereas cathodal stimulation inhibits activity. Effects on cortical excitability can last beyond the stimulation period. The currents involved are not considered sufficiently strong to induce action potentials but rather are likely to alter membrane potentials, *i.e*. the procedure may alter synaptic plasticity by strengthening or weakening synaptic transmission. Candidate targets for non-invasive brain stimulation (NIBS) in EDs include brain regions/circuitry associated with cognitive control, negative and positive valence, and social processing [13]. For pragmatic accessibility reasons, many NIBS studies have targeted the dorsolateral or dorsomedial prefrontal cortex.

It is beyond the scope of this paper to review extensively the evidence relating to potential mechanisms of action underpinning different neurostimulation techniques. The interested reader may wish to consult the following reviews: George and Aston-Jones [17]; Giordano *et al*. [18]; Lipsman *et al*. [19]; and Philip *et al*. [16]. However, there has recently been much interest in the role of learning in the development/maintenance of psychiatric disorders, including EDs, and also in the role of new learning in treatment [20, 21]. Thus, it is appropriate to consider the neural underpinnings of memory as a potential target for neurostimulation and we briefly elaborate on this here. Of particular clinical interest is reconsolidation, the process by which memories can be made labile at the time of their reactivation [22, 23], and is therefore increasingly being used as a treatment target. The rationale is based on the broad assumption that psychological interventions are most effective when the links between pathological stimuli and maladaptive emotional responses/thinking/behaviours are broken [20]. This is, of course, the objective of exposure treatments [24, 25], however, another approach is to update emotional memories by changing their salience during their reconsolidation [26]. This can be done using either psychological [27-29] or pharmacological approaches [30-33]. Importantly, in the present context, there are reports that neurostimulation alters memory reconsolidation, and some investigators have begun to assess the effects of tDCS on reconsolidation [34]. The underlying mechanisms centre around the idea that new memories arise when the balance between excitatory (glutamatergic) and inhibitory (GABA-ergic) (E-I) firing patterns are disrupted [34, 35], as can be promoted by neurostimulation. What is of particular interest here is that very different treatment approaches, such as the ones described above, may share common mechanisms; it is possible that they may all change the balance between E-I systems. On the basis of such studies, our view is that future research on mechanisms related to neurostimulation will need to identify the neurotransmitter systems which are the key targets, *e.g*. 5-hydroxytryptamine (in relation to affect), dopamine (in relation to reward and habits) and/or glutamate/GABA (E-I) (in relation to memory/synaptic plasticity).

Table 1. Common modern neurostimulation techniques.

Type	Invasiveness	Mechanism of Action
Transcranial magnetic stimulation (TMS)	Non-invasive	Electromagnetic induction leads to modulation of underlying cortex and neural activity.
Transcranial direct current stimulation (tDCS)	Non-invasive	Weak current alters neuronal excitability. Neural effects depend on the direction of current.
Deep brain stimulation (DBS)	Invasive	Electrical pulses delivered to specific brain area/circuitry central to condition.

In recent years there has been a surge in interest in neurostimulation techniques and several reasons for this have been identified [16]: Firstly, neurostimulation techniques have the potential for being highly targeted on particular brain regions or networks to alleviate psychiatric symptoms. Secondly, their mechanisms of action differ from those of pharmacotherapy, and thus they offer fresh hope to those who fail to respond to medication. Thirdly, with increasing use of electronic and mobile devices that interface/interact with the human body (*e.g*. smartphones, watches with sensors and apps that monitor individuals' vital characteristics and behaviour), use of medical technologies that interact with the central nervous system may also become more acceptable. Fourth, these techniques, especially NIBS, are seen as having a superior side effect profile compared to ECT and medications. Finally, they have been shown in healthy populations to improve cognition and a range of non-specific symptoms (*e.g*. stress). It is hoped that these kinds of changes will be achieved in psychiatric patients.

We previously systematically reviewed the literature related to DBS, rTMS, tDCS and vagus nerve stimulation (VNS) in human and animal studies [36], focusing on the effects of these techniques on ED symptoms, such as food intake and body weight and related behaviours, in people with clinical EDs, related analogue populations, in those with other psychiatric or neurological disorders and also in animals. Here, we have conducted a more selective search, focusing only on human studies, specifically in people with EDs (and related analogue populations), identifying updates in the literature from 2013 to the present. Although VNS is receiving a resurgence of interest in other disorders, such as depression [37, 38], we decided not to include this in the present review, as to the best of our knowledge, no studies have focused on using VNS in EDs.

2. METHODS

A systematic review was conducted, following the recommendations outlined in the PRISMA guidance [39] and using a similar search strategy to our previous review [36], so as to be able to combine the identified studies.

2.1. Selection Criteria

We included articles in English that investigated the effects of a form of neurostimulation on eating- and weight-related outcomes, for example ED symptoms, food cravings, food intake, and BMI. Studies focusing on clinical EDs and related analogue populations (which in this case refers to individuals who display sub-clinical disordered eating behaviours *e.g*. people with frequent food cravings, restrained eaters, sub-clinical binge eating disorder) were included. Randomised control trials (RCTs), clinical studies, case series and single case reports were eligible for inclusion.

Studies were excluded if: (i) they did not report on changes to eating-related outcomes as a result of neurostimulation; (ii) the sample did not include participants with clinical EDs or related analogue populations (which in this case refers to samples in which sub-clinical disorder eating behaviours, such as food cravings or restriction, are experimentally elicited in healthy individuals); (iii) the sample comprised of animals; and (iv) they used less common methods of neurostimulation (*e.g*. VNS). Review articles, meta-analyses, conference proceedings/abstracts, editorials, letters, book chapters, and unpublished theses were also not included.

2.2. Search Strategy

Three electronic databases (PubMed, ISI Web of Science Core Collection, and PsycINFO *via* Ovid SP) were searched from 1st January 2013 until 14th August 2017 using the following keywords, which were mapped to Medical Subject Headings with the Explode function where possible: eating disorder*, anorexia, anorexi*, bulimia, bulimi*, binge eat*, eating*, food in combination with brain stimulation, DBS, TMS, transcranial magnetic stimulation, tDCS, transcranial direct current stimulation, transcranial stimulation. These searches were supplemented by internet searches and hand searches of reference lists of potentially relevant papers and reviews. Citation tracking in Google Scholar was also performed. The initial search yielded 614 abstracts.

Titles and abstracts of retrieved publications were assessed for relevance, and duplicates were removed. Title and abstracts were screened and based on these, papers that were deemed highly unlikely to be relevant were disregarded. Full-text versions of the remaining articles were then obtained and screened according to the pre-specified eligibility criteria. All papers that did not meet the inclusion criteria were excluded, with the reasons documented (Fig. **1**). The entire search process was conducted independently by two reviewers (B.D. and S.B) and disagreements at the final stage were resolved by consensus. The PRISMA flow diagram of the update search is presented in Fig. (**1**). The paper by McClelland *et al*. [40] reports an extension and longer term follow-up of an earlier paper by McClelland *et al*. [41] and the papers by Lipsman *et al*. [42], Hayes *et al*. [43], and Lipsman *et al*. [44] refer to different aspects of the same and increasingly extended sample. In both cases we counted these papers as relating to one study. The findings of the update search were collated together with eligible papers from our earlier review [36]. Of note, four of the eligible studies had already been identified in our earlier review: Lipsman *et al*. [42]; McLaughlin *et al*. [45]; Van den Eynde *et al*. [46]; and Wu *et al*. [47].

2.3. Data Extraction

The principal reviewer (B.D.) extracted data from all included studies into an electronic summary table, which was then checked by another reviewer (S.B.). Information collected related to the sample characteristics, study design, neurostimulation technique and protocol, target brain area, and relevant findings. A narrative synthesis is presented due to the methodological diversity of the included studies.

3. RESULTS

We identified 18 new studies in the update search (n=368 participants) that met the inclusion criteria for this review, in addition to 14 studies identified in our earlier review [36], yielding a total number of 32 studies to be included in the current review (total n=526 participants). Eight of these studies were conducted in analogue samples of people with food cravings (n=160 participants), 13 in AN patients (n=148 par-

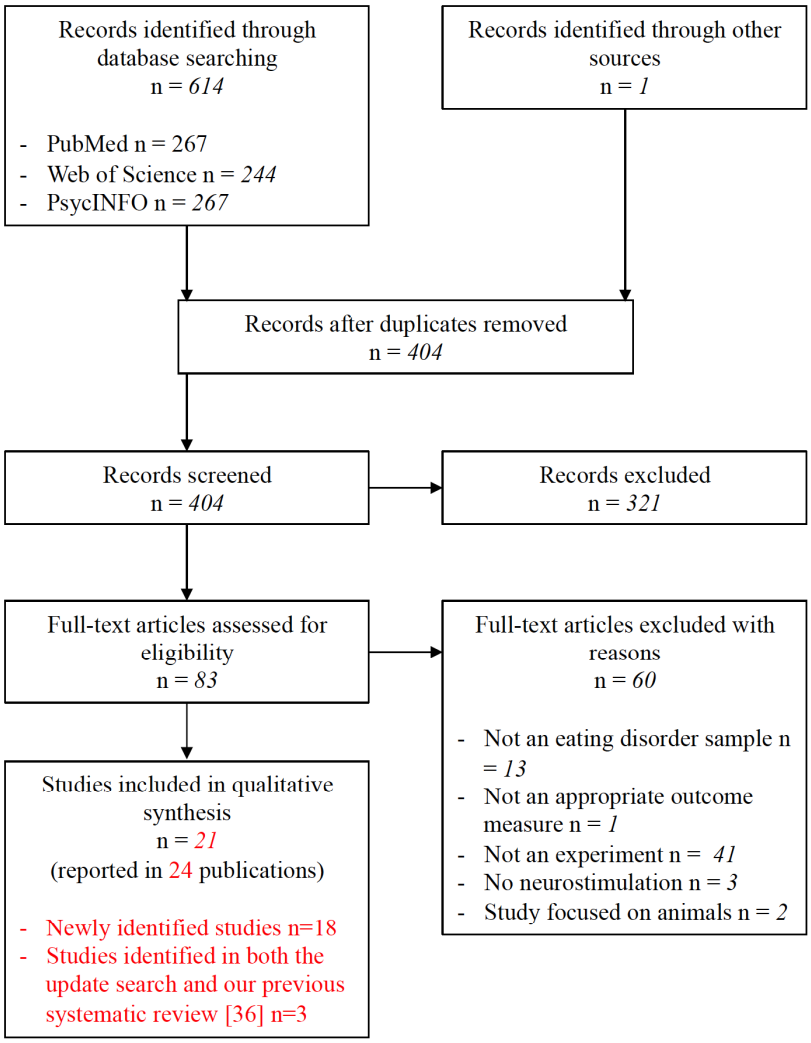

Fig. (1). PRISMA flow diagram of update search (1st January 2013 until 14th August 2017).

ticipants), 9 in BN patients (n=187 participants) and 2 in BED patients (n=31 participants). One study included both AN-binge/purge subtype (AN-BP) and BN patients [48], which for the purposes of this review was reported alongside studies in people with BN. The following neurostimulation techniques were investigated: DBS (7 studies), rTMS (17 studies) and tDCS (8 studies). Tables **2**-**4** show the newly identified studies, together with those that we identified in our earlier review [36].

3.1. Studies in Analogue Samples of Healthy People with Food Craving

We identified 8 small controlled trials; three applied high or low-frequency rTMS (n=59 participants), one of which used continuous theta burst stimulation (cTBS), a variant of rTMS (n=21 participants), and 5 applied tDCS (n=101 participants) to either the left or right DLPFC in people with frequent food cravings (Table **2**). Six of these studies used a cross-over design. With the exception of one study, which delivered 5 sessions of tDCS over one week [49], all others only delivered 1 session or 1 session per condition. The cTBS study used this method as an illness probe and as hypothesised found an increase of snack food craving after active cTBS, but not after sham [50]. All other studies found an effect of the active condition on reducing general food-craving, sweet food craving, or on valuation of foods. Out of four studies that reported the effects of neurostimulation on actual food consumption, two found that the active condition seemed to reduce this [51, 52], whereas the others found no difference [53, 54]. The one study that used a multi-session design, found five sessions of active tDCS, but not sham tDCS, to the right DLPFC (anode right/cathode left forehead) to reduce food cravings [49]. This improvement was observed 30 days post-treatment. Compared to sham tDCS, active tDCS also decreased craving for fast food and sweets (but not carbohydrates).

3.2. Studies in People with Anorexia Nervosa

We identified 13 studies investigating the effects of neurostimulation in patients with AN (Table **3**).

3.2.1. DBS

Seven case studies or series were identified that used DBS to treat chronic or treatment-refractory AN. The largest

Table 2. Research studies assessing the effects of neurostimulation in analogue samples of people with food craving.

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Repetitive transcranial magnetic stimulation								
Lowe *et al*. [50]	21	Healthy females with strong and frequent food cravings for experimental foods	cTBS	Double-blind sham-controlled within-subjects crossover Conditions: (i) real cTBS (ii) sham cTBS	Left DLPFC Located using 10–20 EEG system (F3 for left DLPFC)	3 stimuli at 50 Hz repeated at 5 Hz for a total of 600 stimuli for 40 seconds, 80% MT 1 session per condition	After active cTBS, participants reported larger increases in snack food cravings and consumed more snack foods than after sham.	Performance on a Stroop task was more impaired after active cTBS than after sham. The aim of this study was to examine the relationship between DLPFC function and dietary self-control.
Barth *et al*. [55]	10	Healthy adults with high food cravings	rTMS	Double-blind sham-controlled within-subjects crossover Conditions: (i) real rTMS (ii) sham rTMS	Left DLPFC Located using the 5 cm anterior method	10 Hz, 15 minutes, 100% MT, 3000 pulses 1 session per condition	No difference between real and sham rTMS in reducing cravings.	-
Uher *et al*. [56]	28	Healthy adults with high food cravings	rTMS	RCT; parallel group design Conditions: (i) real rTMS (ii) sham rTMS	Left DLPFC Located using the 5 cm anterior method	10 Hz, 20 minutes, 110 % MT, 1000 pulses 1 session	Food cravings during food exposure remained stable after real rTMS and increased after sham rTMS.	-
Transcranial direct current stimulation								
Ljubisavljevic *et al*. [49]	30	Healthy adults with high food cravings Right handed	tDCS	RCT Conditions: (i) Active tDCS: anode right/cathode left (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 1st session.
Kekic *et al*. [53]	20	Healthy female adults with high food cravings	tDCS	Double-blind sham-controlled within-subjects crossover Conditions: (i) Active tDCS: anode right/cathode left (ii) Sham tDCS	Right DLPFC Located using 10–20 EEG system (F4 for right DLPFC, F3 for left DLPFC)	2mA; 20 minutes 1 session per condition	Active tDCS did not alter global food craving scores or actual food consumption compared to sham tDCS, although it did lead to a reduction in craving for sweet foods (but not savoury).	The study also investigated the effects of tDCS on temporal discounting (TD, a measure of choice impulsivity). No differences were seen in TD after real vs sham tDCS. Participants who showed more reflective choice behaviour were more susceptible to the anti-craving effects of tDCS than those that displayed more impulsive choice behaviour.

(Table 2) contd….

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Transcranial direct current stimulation								
Lapenta *et al*. [51]	9	Healthy female adults with food cravings	tDCS	Single-blind sham-controlled within-subjects crossover Conditions: (i) Active tDCS: anode right/cathode left (ii) Sham tDCS	Right DLPFC Located using 10–20 EEG system (F4 for right DLPFC, F3 for left DLPFC)	2mA; 20 minutes 1 session per condition	Active tDCS reduced food craving and the amount of calories ingested, compared with sham tDCS.	This study included assessment of evoked potentials in a Go/No-go Task that contained pictures of food and furniture (a control visual stimulus). Active vs sham tDCS, reduced the frontal N2 component and enhanced the P3a component of responses to No-go stimuli, regardless of the stimulus condition (food, furniture). Both N2 and P3a are thought to be markers of inhibitory control.
Goldman *et al*. [54]	19	Healthy adults with food cravings	tDCS	RCT, cross-over, blinded Conditions: (i) Active tDCS: anode right/cathode left (ii) Sham tDCS	DLPFC Located using 10–20 EEG system (F3 for left DLPFC; F4 for right DLPFC)	2mA, 20 minutes 1 session per condition	Food cravings reduced in both conditions; however, percentage change was significantly greater in active tDCS. Active tDCS reduced food cravings for sweet foods and carbohydrates more than sham. No difference between groups in amount of food ingested.	-
Fregni *et al*. [52]	23	Healthy adults with food cravings	tDCS	RCT, cross-over, double-blinded Conditions: (i) anode left/cathode right (ii) anode right/cathode left (iii) Sham tDCS	DLPFC Located using 10–20 EEG system (F3 for left DLPFC; F4 for right DLPFC)	2mA, 20 minutes 1 session per condition	Craving of viewed foods decreased with anode right/cathode left, remained stable with anode left/cathode right and increased after sham. Subjects fixated (eye tracking) on food related pictures less after anode right/cathode left. Subjects consumed less food after both types of active stimulation.	-

Abbreviations: cTBS - continuous theta burst stimulation, a variant of rTMS that transiently inhibits cortical activity; DLPFC - dorsolateral prefrontal cortex; EEG - electroencephalography; Hz - Hertz; MT - motor threshold; rTMS - repetitive transcranial magnetic stimulation; RCT - randomised controlled trial; tDCS - transcranial direct current stimulation; mA - milliAmpere; TD - temporal discounting.

series administered bilateral stimulation to the SCC in 16 patients [44]. This was an extension of an earlier series of 6 patients [42]. DBS treatment increased BMI in the year following surgery. Furthermore, symptoms of depression and anxiety also improved post-surgery. Two patients asked to have their device removed for reasons that were not entirely

clear. Whilst 10 out of 16 patients experienced at least one adverse event, only one was a DBS-related surgical site infection, most others were related to the underlying illness. Within this study [44], PET imaging identified significant changes in glucose metabolism in brain structures implicated in AN at 6 and 12 months follow-ups, compared with baseline, suggesting that DBS can directly affect AN-related brain circuitry. An associated study in 8 patients who were part of this DBS series used diffusion MRI and deterministic multi-tensor tractography to compare anatomical connectivity and microstructure in SCC-associated white matter tracts [43]. Compared to healthy controls, AN patients displayed widely distributed heterogeneous differences in SCC connectivity.

Three case series from China (n=12) [47, 57, 58] used nucleus accumbens DBS to treat severe AN. Of note, most of the patients included in these series were adolescents or young adults with short illness duration. Whilst all three series emphasised the benefits of DBS in terms of weight gain, psychological outcomes and longer-term follow-up data were not always reported. Three other single case studies used DBS in enduring treatment-refractory AN with comorbid severe depression or obsessive compulsive disorder, targeting the SCC [59], VC/VS [45] or the bed nucleus of the stria terminalis [60]. In the first two of these cases, ED symptoms remitted and the patient's BMI returned to normal or near normal [45, 59]. In the latter case, surgery reduced anxious and obsessive thoughts surrounding food and eating, stabilized food intake, reduced self-induced vomiting and improved depression symptoms, but without any improvement in BMI [60].

3.2.2. rTMS

One single case study [61], two case series [40, 41, 46] and two RCTs [62, Schmidt, personal communication; for protocol [63] assessed the effect of rTMS on AN symptoms. Two of these used single session designs [46, 62], the remainder used multi-session designs. All studies targeted the left DLPFC. Van den Eynde *et al*. [46] conducted a pilot study of a single-session of real rTMS finding that it was generally well-tolerated and reduced some of the core symptoms of AN. No change in urge to restrict food or in mood was found. Building on these findings, we conducted a sham-controlled single session RCT [62]. Patients receiving real rTMS (compared to the sham group) showed an improvement in core AN symptoms (urge to restrict, feeling full, feeling fat) post-rTMS and at a 24-hour follow-up. Real rTMS was also found to encourage more prudent decision-making in a temporal discounting task.

The first report of therapeutic use of rTMS in a case of severe AN and depression was published by Kamolz *et al*. [61]. A total of 41 sessions of left DLPFC rTMS were delivered. The patient showed improvements in both ED and depressive symptoms after an initial course of 10 rTMS sessions. However, this was followed by deterioration and so, further sessions of rTMS were delivered, with further improvement of depression and ED symptoms. McClelland *et al*. [40, 41] conducted a case series (n=5) assessing the effect of a treatment course (20 sessions) of real rTMS in patients with severe and enduring AN. At post-treatment significant improvements in ED and affective symptoms were observed. While further improvements were seen at 6-months post-treatment (3/5 participants deemed 'recovered' on the Eating Disorders Examination Questionnaire [64]), by 12-months post-treatment, the therapeutic effects had waned and participants had lost some weight compared to baseline. Since then we have completed a sham-controlled feasibility RCT of 20 sessions in 34 patients with severe and enduring AN [Schmidt, personal communication; for protocol see 63]. Cognitive and neural correlates of rTMS treatment are also being examined. Patient retention in the study and treatment completion rates were high. Whilst between group differences at post-treatment were small, at 3 months post-treatment, there were between-group differences of medium effect size in depression, stress and obsessive compulsive symptoms, all favouring the active treatment. Group differences in ED symptoms and BMI were of negligible effect at both post-treatment and follow-up.

Only one study reported on the effect of 10 sessions of tDCS in an open-label pilot study in patients with AN [65]. Variable responses to the treatment were observed: scores on eating and depression questionnaires improved in three patients at post-treatment and follow-up, in two participants improvements were seen at the end of treatment but scores returned to baseline at one-month post-treatment, one participant showed improvements only in depression, and one participant showed no improvements following treatment.

3.3. Studies in People with Bulimia Nervosa

We identified nine studies in patients with BN, eight of these applied rTMS (n=148 participants) and one applied tDCS (n=39 participants) (Table **4**).

3.3.1. rTMS

The rTMS studies included 5 single case studies/case series and three RCTs, stimulating either the left DLPFC or the dorsomedial prefrontal cortex (DMPFC). Findings from case studies/series were promising in that they all noted reductions in urge to eat, and in some studies reductions in actual binge and/or purge episodes were reported [48, 66-69]. Of note, one small case series of rTMS to the left DLPFC studied left-handed patients and found that their mood deteriorated after 1 session of rTMS [67], whereas in a comparison group of right-handed BN patients receiving left DLPFC rTMS, their mood improved. A sham-controlled RCT of one session of rTMS found a decrease in self-reported urge to eat and binge eating (24-hours post-treatment) [70]. An associated study [71] in a subgroup of participants found that real rTMS reduced salivary cortisol levels compared to sham.

Multi-session designs (10-20 sessions) were used in one larger case series [48] and two RCTs [72, 15 sessions, 73, 10 sessions]. Dunlop *et al*. [48] assessed the effect of 20 sessions of DMPFC rTMS on binging and purging in a transdiagnostic sample comprised of patients with BN or AN-BP. Purge frequency, global ED symptom scores and depression scores had significantly reduced at the 4-week post-treatment follow-up. Just over half of the participants were classed as treatment responders with a >50% reduction in binge and

Table 3. Research studies assessing the effects of neurostimulation in people with anorexia nervosa.

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Deep brain stimulation								
Blomstedt *et al*. [60]	1	Adult female with chronic AN and severe MDD	DBS	Single case	Bed nucleus of the stria terminalis (BNST)	Bilateral stimulation of 130 Hz, 120 μs 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 were initially implanted in the medial forebrain bundle. Due to side effects, stimulation was turned off. Re-operated on for DBS of the BNST two years after first operation.
Lipsman *et al*. [44]	16	Adults with enduring AN	DBS	Open-label trial	Subcallosal cingulate	Bilateral stimulation of 130 Hz, 90 μs 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.	This study is an extension of Lipsman *et al*. [42] and Hayes *et al*. [43]. PET imaging identified significant changes in glucose metabolism in several brain structures implicated in AN at 6 and 12 months follow-ups, compared with baseline.
Hayes *et al*. [43]	8	Female adults with treatment-refractory DSM-IV AN	DBS	Open-label trial	Subcallosal cingulate	As in Lipsman *et al*. [44]	Compared to healthy controls widely distributed differences in SCC connectivity were found in AN patients.	These cases are included in the Lipsman *et al*. [44] series. The study used diffusion magnetic resonance imaging and deterministic multitensor tractography to compare anatomical connectivity and microstructure in SCC-associated white matter tracts.
Lipsman *et al*. [42]	6	Female adults with chronic or treatment resistant DSM-IV AN	DBS	Open-label trial	Subcallosal cingulate	As in Lipsman *et al*. [44]	Included in Lipsman *et al*. [44]	These cases are included in the Lipsman *et al*. [44] series.
Wang *et al*. [57]	2	Female adults with AN	DBS	Case series	Nucleus accumbens	Bilateral stimulation of 135-185 Hz, 120-210 μs pulse width, and 2.5-3.8 V to the nucleus accumbens	Pre-operative BMI: Case 1 –13.3 Case 2 – 12.9 BMI at 1 year post-op: Case 1 – 18 Case 2 – 20.8	Patient's illness duration was 2 and 3 years respectively. Depression, anxiety and obsessive compulsive symptoms reduced significantly from pre-op to 1 year post-op.

(Table 3) contd….

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Deep brain stimulation								
Wu *et al*. [47]	4	Female adolescents with AN with failure to respond to standard psychiatric treatment programme of at least 12 month	DBS	Open-label trial	Nucleus accumbens	Bilateral stimulation of 180 Hz, 90 μs pulse width and >6 V to the nucleus accumbens	Average increase of 65% body weight from baseline to post-surgery follow-up (mean 38 months). Menstruation restored in all participants following surgery.	Patients had short illness duration (13 to 28 months) and BMIs between 10 to 13.3 kgs/m^2 at pre-treatment. Improvements in anxiety and obsessive-compulsive symptoms. No definition is given of the standard psychiatric treatment that patients had previously failed to respond to.
Zhang *et al*. [58]	6	Adolescent Patients with restricting type AN (age 13 to 17)	DBS	Case series	Nucleus accumbens	DBS protocol not described	Follow-up data at 1 month post-DBS is available for 4 out of 6 patients. All 4 showed improvements in BMI. No longer term follow-up provided.	Patients had a short illness duration (13-42 months) and BMIs between 11.2 and 13.5 at pre-treatment. All had previous unsuccessful behavioural and medication treatments. The main focus of the study was on PET imaging. Compared to healthy controls AN patients showed baseline hypermetabolism in the frontal lobe, hippocampus, and lentiform nucleus. This decreased after DBS.
McLaughlin *et al*. [45]	1	AN and Obsessive compulsive disorder	DBS	Single case report	VC/VS Bilateral	Bilateral stimulation of 120 Hz, 120 μs pulse width and 7.5 V to the VC/VS	Food intake, food variety and body weight were increased. BMI maintained between 18.9 and 19.6 postoperatively.	Symptoms worsened when cathode electrode was added.
Israel *et al*. [59]	1	Adult female with AN and depression	DBS	Single case report	Subgenual cingulate cortex Bilateral	Right-sided intermittent stimulation (2 minutes on/1 minute off) at 130 Hz, 5 mA and 91 μs pulse width to the subgenual cingulate cortex	Remission of ED, no relapse and maintained average BMI of 19.1. Remission from ED persisted despite depressive breakthrough.	-

(Table 3) contd….

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Repetitive transcranial magnetic stimulation								
Schmidt [personal communication; for protocol 63]	34	Females with chronic treatment-refractory DSM-5 AN Right handed	rTMS	Feasibility RCT	Left DLPFC Neuronavigation	20 × 5 s trains/55 s inter-train interval at 10 Hz = 1000 pulses per session; 110% MT ~20 sessions	At 3-month follow-up between-group differences of medium effect size were noted in measures of depression, anxiety, and obsessional symptoms, favouring active rTMS. Changes in eating disorder symptoms were less pronounced.	Neurocognitive (*e.g.* temporal discounting) and neural predictors and correlates of rTMS are also being assessed.
McClelland *et al*. [41] [40]	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	Compared to baseline, at post-treatment, participants showed significant improvements in ED and affective symptoms. Further improvements were seen at 6 months post-treatment.	-
McClelland *et al*. [62]	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.	This study also assessed cognitive (temporal discounting; TD) and biomarkers (salivary cortisol) of rTMS. In relation to TD, there was an interaction trend ($p = 0.060$): real vs sham rTMS resulted in reduced rates of TD (more reflective choice behaviour). Salivary cortisol concentrations were unchanged by stimulation.
Van den Eynde *et al*. [46]	10	Adults with DSM-IV-TR AN Right-handed	rTMS	Pilot study	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	In completers (n=9), based on VAS scales, sensations of "feeling fat" and "feeling full", and "anxiety" decreased between pre- and post-rTMS. No change observed in "urge to restrict" or "urge to eat". No changes in mood following rTMS.	-

(Table 3) contd….

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Repetitive transcranial magnetic stimulation								
Kamolz *et al*. [61]	1	Adult with AN and depression	rTMS	Case report	Left DLPFC Located using 10-20 EEG system (F3)	100 x 2 s trains/10 s inter-train interval at 10 Hz = 2000 pulses per session, 110 % MT 41 sessions	Improvements in depression and ED symptoms after 10 sessions, after deterioration further rTMS sessions were given including maintenance sessions (2 p/week). This resulted in continuing improvement of depression and ED symptoms.	-
Transcranial direct current stimulation								
Khedr *et al*. [65]	7	Adults (n=1 male) with DSM-IV AN	tDCS	Open-label pilot study Active tDCS: anode left / cathode contralateral arm	Left DLPFC Located using 6 cm anterior method	2mA; 20 minutes 10 sessions	Variable response in participants. Significant improvement compared with baseline in the BDI, EDI and EAT at post session and also at one month post-treatment (n=3).	-

Abbreviations: AN - anorexia nervosa; MDD - major depressive disorder; DBS - deep brain stimulation; BNST - bed nucleus of the stria terminalis; Hz - Hertz; µs - micro seconds; V - volts; BMI - body mass index; PET - positron emission tomography; DSM - Diagnostic and Statistical Manual [74, 75]; SCC - subcallosal cingulate; VC/VS - ventral capsule/ventral striatum; ED - eating disorder; rTMS - repetitive transcranial magnetic stimulation; RCT - randomised controlled trial; DLPFC - dorsolateral prefrontal cortex; s - seconds; Hz - Hertz; MT - motor threshold; TD - temporal discounting; VAS - visual analogue scales; tDCS - transcranial direct current stimulation; mA - milliAmpere; EEG - electroencephalography; BDI - Beck Depression Inventory [76]; EDI - Eating Disorder Inventory [77]; EAT - Eating Attitudes Test [78].

purge frequency at follow-up. Whilst in both RCTs [72, 73] there were some improvements in binge-purge symptoms over time, there was no group difference between patients receiving real or sham rTMS.

3.3.2. tDCS

The only study examining the effects of tDCS in patients with BN was a small cross-over study in which two tDCS electrode montages (anode left DLPFC/cathode right DLPFC and in the reverse montage) were compared to sham treatment [79]. The study found that one session of anode right/cathode left active tDCS led to reductions in ED cognitions and improvement in mood, compared to the other active and sham condition. Both active conditions suppressed the self-reported urge to binge eat.

3.4. Studies in People with Binge Eating Disorder

We identified two studies (n=31 participants) (see Table **5**).

3.4.1. rTMS

A case study of a female with refractory BED and comorbid depression found that 20 sessions of high frequency rTMS to the left DLPFC led to a reduction in binge frequency and improvements in the clinical global impression score [80]. Depression and binge eating questionnaire scores also improved.

3.4.2. tDCS

The effects of tDCS were assessed in 30 adults with full or subthreshold BED [81]. Active tDCS (anode right DLPFC/cathode left DLPFC) was found to decrease craving more than sham tDCS for desserts, savoury proteins, and the all-foods category. Interestingly, active tDCS reduced the male participant's craving more than the female's craving for desserts and the all-foods category. Participants ate fewer total kilocalories in the lab after active tDCS compared to following sham tDCS. Active tDCS reduced desire to binge eat 5-6 hours post-stimulation, however, this was observed in the male participants only.

4. DISCUSSION

4.1. Overall Findings

Our review shows that there is an expanding literature on the use of neurostimulation procedures for the treatment of EDs and related eating behaviours (food craving). Compared to our earlier systematic review only 4 years ago, the number of available studies and the number of participants in them, has more than doubled, which is encouraging. However, as yet, the majority of these studies are single case studies, case series, or proof-of-concept experimental studies using single session and cross-over designs. These studies provide preliminary evidence that suggests that neurostimulation has potential for altering disordered eating behaviours, food intake and body weight. Therefore, a strong case can be made for continuing to examine and develop neurostimulation protocols that can be used to treat EDs and which can also be used as illness probes [50].

At this point DBS is arguably the treatment with the strongest theoretical underpinnings and clearest rationale for specific treatment targets. It is also the most invasive of these treatments and as such has been mainly advocated for use in severe and enduring AN. DBS has shown promise in different case series, and can give new hope to this group of

Table 4. Research studies assessing the effects of neurostimulation in people with bulimia nervosa.

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Repetitive transcranial magnetic stimulation								
Gay *et al*. [73]	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.	There were no within group differences from pre-to post treatment in either groups in relation to binge or purge episodes. However, within the active rTMS group there was a borderline significant (p=0.05) reduction in depression symptoms over time.
Sutoh *et al*. [66]	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 ED symptoms was identified.	Using near-infrared spectroscopy, haemoglobin concentration changes in the DLPFC was measured during cognitive tasks (rock-paper-scissors and food picture task), measuring self-regulatory control, both at baseline and after a single session of rTMS. A significant decrease in cerebral oxygenation of the left DLPFC was observed after a single session of rTMS.
Dunlop *et al*. [48]	28	Adults (n=2 male) with DSM-5 BN (n=17) or AN-BP (n=11) Treatment non-responders	rTMS	Case series	DMPFC Neuronavigation	20 × 5 s trains/10 s inter-train interval at 10 Hz = 3000 pulses per session; 120% MT 20 sessions Treatment responders (n=16) received 10 additional sessions	In whole sample, no change in binge frequency but significant reduction in purge frequency. N=16 achieved >50% reduction in binge and purge frequency (responders).	Resting state fMRI data were collected before and after rTMS treatment to identify neural predictors and correlates of treatment response. Enhanced frontostriatal connectivity was associated with being an rTMS responder. In non-responders, frontostriatal functional connectivity was high at baseline, and rTMS suppressed functional connectivity in association with symptomatic worsening.

(Table 4) contd….

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Repetitive transcranial magnetic stimulation								
Downar *et al*. [68]	1	Adult with severe refractory BN and depression	rTMS	Case study	Bilateral DMPFC Neuronavigation	60 x at 5 s trains/10 s inter-train interval at 10 Hz, 3000 pulses; 120 % MT 2 x 20 sessions	Full remission of binge-purging episodes and depression for more than 2 months post-treatment completion; after a significant stressor some ED symptoms returned. These remitted after a 2nd 20 session course of treatment.	-
Van den Eynde *et al*. [67]	7	Adults with BN Left-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	Decrease in reported cravings, but mood deteriorated.	-
Van den Eynde *et al*. [70]	38	Adults with BN Right handed	rTMS	RCT Double blind, parallel groups Conditions: (i) real rTMS (ii) sham rTMS	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	Compared with sham, real rTMS was associated with a decrease in self-reported urge to eat and binge eating (24 hours post-treatment). No difference between groups in hunger, tension, mood and urge to binge eat.	An associated study in 22 participants from the same trial [71] found a reduction of salivary cortisol in patients receiving real, compared to those receiving sham rTMS. Another associated study [82] in 33 trial participants found no effect of rTMS on cognition (selective attention, assessed with a Stroop task).
Walpoth *et al*. [72]	14	Female adults with DSM-IV BN	rTMS	RCT Double blind, parallel groups Conditions: (i) real rTMS (ii) sham rTMS	Left DLPFC Neuronavigation	10 × 10 s trains/60 s inter-train interval at 20 Hz, = 2000 pulses; 120% MT 15 sessions over 3 weeks	Improvement in self-reported binge-purge behaviours, depressive and OCD symptoms in both groups. No difference between real and sham groups.	-
Hausmann *et al*. [69]	1	Adult with BN and depression	rTMS	Case study	Left DLPFC Neuronavigation	10 × 10 s trains/60 s inter-train interval at 20 Hz, = 2000 pulses; 80% MT 10 sessions over 2 weeks	Remission from binge-purge symptoms and almost 50% decrease in depression score at post-treatment.	-

(Table 4) contd….

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Transcranial direct current stimulation								
Kekic *et al*. [79]	39	Adults with DSM-5 BN Right handed	tDCS	RCT Double-blind 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.	The study also assessed temporal discounting (TD), finding that active but not sham tDCS reduced TD behaviour (was associated with more reflective choice behaviour).

Abbreviations: DSM - Diagnostic and Statistical Manual [74, 75]; BN - bulimia nervosa; rTMS - repetitive transcranial magnetic stimulation; DLPFC - dorsolateral prefrontal cortex; s - seconds; Hz - hertz; MT - motor threshold; ED - eating disorder; AN-BP - anorexia nervosa binge/purge subtype; DMPFC - dorsomedial prefrontal cortex; tDCS - transcranial direct current stimulation; mA - milliAmpere; EEG - electroencephalography; RCT - randomised controlled trial; OCD - obsessive compulsive disorder; TD - temporal discounting.

Table 5. Research studies assessing the effects of neurostimulation in people with binge eating disorder.

Author	*N*	Sample	Treatment Type	Design	Area	Protocol	Findings	Comments
Repetitive transcranial magnetic stimulation								
Baczynski *et al*. [80]	1	Adult female with refractory BED and co-morbid depression	rTMS	Case report	Left DLPFC Located using 10–20 EEG system (F3 for left DLPFC)	20 × 4 s trains/26 s inter-train interval at 10 Hz = 2400 pulses per session; 120% MT 20 sessions, over 4 weeks and 2 days	At the end point of rTMS (3 days post-treatment), binge eating episode/week had reduced to 0, clinical global impression score had reduced from 6 pre-treatment to 1 post-treatment. BDI and BES scores also reduced (approx. 40 to 25).	-
Transcranial direct current stimulation								
Burgess *et al*. [81]	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.

Abbreviations: BED - binge eating disorder; rTMS - repetitive transcranial magnetic stimulation; DLPFC - dorsolateral prefrontal cortex; s - seconds, Hz - hertz; MT - motor threshold; BDI - Beck Depression Inventory [76]; BES - Binge Eating Scale [83]; tDCS - transcranial direct current stimulation; mA - milliAmpere.

patients who have often received multiple unsuccessful treatments. However, several small studies from China have applied DBS in adolescent patients with very severe, recent onset of illness (and therefore good prognosis). Whilst these were clearly cases with often alarmingly low BMIs, one cannot help considering whether in a different healthcare system with greater access to specialist ED in-patient treatment programmes and associated family-based treatments, some of these cases would have recovered with the help of less invasive treatments [84, 85].

To date only 3 parallel group RCTs using rTMS as treatment, *i.e*. applying multi-session protocols, have been reported. All of these used high frequency (excitatory) rTMS and stimulated the left DLPFC. All of these are small trials. Two of these [72, 73], which were focused on BN, did not

show an effect of rTMS on ED outcomes at post-treatment assessment. The third is a feasibility trial in patients with severe and enduring AN and this has shown promising results at 3-month follow-up, with group differences of medium effect sizes mainly in relation to improvement of mood [Schmidt, personal communication; for protocol see 63]. Key differences between these studies lie in the number of rTMS sessions offered, the way the stimulation target was determined (with or without MRI guidance) and their assessment schedule. Compared to the AN study, the two BN studies offered fewer sessions (10 or 15) and did not determine the stimulation target with MRI guidance. Moreover, neither of the two BN studies included a follow-up and only immediate post-treatment effects were assessed. In contrast, in the AN study, the largest changes were seen at the 3 month follow-up point. This delay in action is something we had previously observed in a small case series of AN patients treated using the same protocol [40]. It is also known from rTMS trials in depression [86, 87].

Despite the ease of use of tDCS, this procedure/technique has to date been used mainly in analogue populations in relation to food craving (5 studies), with just one small case series in AN and two small cross-over proof-of-concept trials in BN and BED. Given that this is by far the most accessible and easy to use method, this is somewhat surprising.

4.2. Cognitive, Neural and Hormonal Correlates and Predictors of Neurostimulation Treatments

In this review, we have focused predominantly on ED and related clinical outcomes. However, there is a growing literature in healthy and clinical populations on the neurocognitive and biological (neural, immunological, electrophysiological, and hormonal) effects of neurostimulation treatments [88]. Only a handful of studies have examined these effects in relation to neurostimulation of EDs. As far as we are aware only two studies assessed the effects of rTMS on salivary cortisol in BN [71] and AN [62] with the former finding an effect, the latter not. Several neuro-cognitive tasks have been studied, such as temporal discounting, assessing choice impulsivity [53, 62; Schmidt, personal communication, 79]; Stroop tasks [50, 82]; the Go-No-go Task [50, 51] and a 'rock-paper-scissors' task [66]. All of these are thought to assess elements of self-regulatory or inhibitory control. These various neurocognitive studies do not produce consistent evidence for the effects of neurostimulation on executive function. For example, Kekic *et al*. [79] and McClelland *et al*. [62], using temporal discounting, have produced data which are indicative of increased self-regulation following neurostimulation (tDCS in BN and rTMS in AN respectively). Somewhat in agreement with this is the report by Lowe *et al*. [50], in that decreasing cortical activity using cTBS diminished inhibitory control in food cravers as measured using a Stroop Task. On the other hand, Van den Eynde *et al*. [82] found no effect of rTMS on Stroop performance in patients with BN. At this point, it is not possible to make definitive statements on how and if executive function is altered by neurostimulation, even when one is stimulating an area known to be involved in self-regulatory and inhibitory control (*i.e*. DLPFC). Until the effects of neurostimulation of the DLPFC on executive function are more established, it is not possible to determine whether effects on executive function mediate the effect of neurostimulation on clinical change in ED symptoms.

A limited number of studies have included a neuroimaging component and hence the field is in its infancy. Two DBS studies have used PET [44, 58] and one diffusion tensor imaging [43], two rTMS studies [48; Schmidt, personal communication] have used functional MRI and one has used near-infrared spectroscopy (NIRS) [66], identifying stimulation-related changes in brain metabolism and neural connectivity. Both PET-based studies reported significant and quite widespread changes in brain glucose metabolism following DBS [44, 58], but simple conclusions on the mode of action do not appear to be obvious at this point. Findings from Dunlop *et al*. [48] suggest that treatment responders exhibit an increase in frontostriatal functional connectivity following rTMS treatment; however, in those who do not respond these increases do not occur. Such findings are broadly consistent with "top down-bottom-up" neural models of eating disorders which are centred on frontostriatal circuitry [4, 9].

All in all, as can be seen from the above studies, combining data on cognitive, neuroimaging, other biological markers and neurostimulation data are as yet in their infancy in EDs compared, for example, to depression. In future, such studies in EDs may be able to identify distinct endophenotypes, associated with differential responses to interventions at both the cognitive/biological/neural and the clinical level. In this way, 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 neurostimulation [48].

4.3. Safety and Acceptability

In general, NIBS seems to be safe and acceptable to patients [89-91]. Potential risks include those that are device-related (*e.g*. seizure risk (rTMS) or skin irritation/burn (tDCS)), adverse cognitive effects and interference with psychiatric treatment [16]. A systematic review of tDCS studies found similarly low drop-out rates for real and sham tDCS [89]. However, these authors noted that the quality of adverse events reporting was low in most studies. Very limited research on issues of safety and acceptability has been conducted in relation to EDs [92].

4.4. Ethical Considerations

Questions over the ethical implications of these neurostimulation techniques have mainly focused on DBS rather than on NIBS, given the invasiveness of DBS and its use in highly vulnerable patients, such as adolescent patients or physically very frail patients with severe and enduring AN. In both cases the capacity for making health-related decisions may be impaired. Additionally, desperate families may push their loved one towards agreeing to DBS. Ethicists have also raised concerns that DBS or NIBS might be perceived as *'mind control',* increasing patients' helplessness and reducing their sense of authenticity [93, 94]. 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 [95, 96]. In a small case series of therapeutic rTMS in AN, patients were asked about their experience [40]. They talked about greater cognitive clarity, flexibility & improved mood. Altered authenticity or agency was not mentioned by any of the participants. Recently a neuroethics framework for the use of DBS in AN has been published [97].

4.5. Future Directions

Whilst the evidence suggests that neurostimulation treatments have significant potential, both as interventions in the treatment of EDs and as probes of illness mechanisms, much of this potential is still waiting to emerge. There is still a considerable amount that needs to be learnt about patient selection, intervention parameters, treatment targets and how to optimise protocols. For example, protocol optimisation will require a substantial amount of experimental work in order to address issues such as target selection, frequency, intensity and duration, and even the type of neurostimulation. Furthermore, much more needs to be learnt about neurocognitive, neural and other biological predictors and correlates of outcome, as this may help to individualise protocols and deliver personalised treatment. Progress is also being made in relation to developing a rationale for use of neurostimulation treatments, substantially based on evolving neural models of EDs [13], including the role of memory and its reconsolidation in the development and treatment of EDs. 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.

Neurostimulation 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 [13]. 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 [98]. Other promising neurotechnologies, such as functional MRI neurofeedback [99] or vagus nerve stimulation, as yet have not been explored in relation to EDs.

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. However, given the limited research in this field, it is not advised that individuals make use of these neurostimulation technologies without supervision from an experienced therapist.

Finally, we have reported elsewhere [100, 101] that several large scale trials of neurostimulation treatments of EDs are forthcoming, *i.e.* registered with national and international trial registries. Several of these are transdiagnostic and/or target specific ED symptoms (*e.g.* binge-eating or body image problems). Thus over the next few years, we are likely to see an explosion of knowledge in this area.

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CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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