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Title: 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.

Keywords: anorexia nervosa, bulimia nervosa, binge eating disorder, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation, neurostimulation

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) [e.g. 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) [for review see 4, 5-8] and to a lesser extent on bulimia nervosa (BN) [for review see 9]. However, there is increasing interest in binge eating disorder (BED) and in obesity [e.g. 10, 11]. There is also interest in the development of spectral models that can accommodate a transdiagnostic framework for these problems [e.g. 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 [e.g. 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 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 deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (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.

INSERT TABLE 1 HERE

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 [e.g. 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 [e.g. 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 [e.g. 27, 28, 29] or pharmacological approaches [e.g. 30, 31-33]. 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-HT (in relation to affect), DA (in relation to reward and habits) and/or glutamate/GABA (E-I) (in relation to memory/synaptic plasticity).

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 relating 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.

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.

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.

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 (see 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 Figure 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].

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.

INSERT FIGURE 1 HERE

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 participants), 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].

Studies in analogue samples of healthy people with food craving

We identified 7 small controlled trials; three applied high or low-frequency rTMS (n=59 participants), one 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 (see 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 [51, 52], two found that the active condition seemed to reduce this, 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).

INSERT TABLE 2 HERE

Studies in people with anorexia nervosa

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

DBS: Seven case studies or series were identified that used DBS to treat chronic or treatment-refractory AN. The largest 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, 55, 56] 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 [57], VC/VS [45] or the bed nucleus of the stria terminalis [58]. In the first two of these cases, ED symptoms remitted and the patient's BMI returned to normal or near normal [45, 57]. 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 [58].

rTMS: One single case study [59], two case series [40, 41, 46] and two RCTs [60, Schmidt, personal communication; for protocol see 61] assessed the effect of rTMS on AN symptoms. Two of these used single session designs [46, 60], 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 [60]. 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. [59]. 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. [41] [40] 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), 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 61]. 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 [62]. 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.

INSERT TABLE 3 HERE

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) (see Table 4).

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, 63-66]. 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 [64], 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) [67]. An associated study [68] 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 [69, 15 sessions, 70, 10 sessions]. Dunlop et al. [48] assessed the effect of 20 sessions 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 purge frequency at follow-up. Whilst in both RCTs [69, 70] there were some improvements in binge-purge symptoms over time, there was no group difference between patients receiving real or sham rTMS.

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 [71]. 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.

INSERT TABLE 4 HERE

Studies in people with Binge Eating Disorder

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

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 [72]. Depression and binge eating questionnaire scores also improved.

tDCS: The effects of tDCS were assessed in 30 adults with full or subthreshold BED [73]. 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.

INSERT TABLE 5 HERE

Discussion

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. Overall, 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 [e.g. 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 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 [e.g. 74, 75].

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 [69, 70], which were focussed 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 61]. 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 [76, 77].

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.

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 neuro-cognitive and biological (neural, immunological, electrophysiological, and hormonal) effects of neurostimulation treatments [e.g. 78]. 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 [68] and AN [60] with the former finding an effect, the latter not. Several neuro-cognitive tasks have been studied, such as temporal discounting, assessing choice impulsivity [53, 60; Schmidt, personal communication, 71]; Stroop tasks [50, 79]; the Go-No-go Task [50, 51] and a 'rock-paper-scissors' task [63]. 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. [71] and McClelland et al. [60], 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 by 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. [79] 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, 56] 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) [63], 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, 56], 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 [e.g. 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].

Safety and Acceptability

In general, non-invasive brain stimulation seems to be safe and acceptable to patients [e.g. 80, 81, 82]. 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 [80]. 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 [e.g. 83].

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 [84, 85]. 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 [86, 87]. 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 neuro-ethics framework for the use of DBS in AN has been published [88].

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 [89]. Other promising neurotechnologies, such as functional MRI neurofeedback [90] 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 [91, 92] 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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