REVIEW

A Systematic Review of the Effects of Neuromodulation on Eating and Body Weight: Evidence from Human and Animal Studies

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Abstract

Background: Eating disorders (ED) are chronic and sometimes deadly illnesses. Existing treatments have limited proven efficacy, especially in the case of adults with anorexia nervosa (AN). Emerging neural models of ED provide a rationale for more targeted, brain-directed interventions.

Aims: This systematic review has examined the effects of neuromodulation techniques on eating behaviours and body weight and assessed their potential for therapeutic use in ED.

Method: All articles in PubMed, PsychInfo and Web of Knowledge were considered and screened against a *priori* inclusion/exclusion criteria. The effects of repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation, vagus nerve stimulation (VNS) and deep brain stimulation (DBS) were examined across studies in ED samples, other psychiatric and neurological disorders, and animal models.

Results: Sixty studies were identified. There is evidence for ED symptom reduction following rTMS and DBS in both AN and bulimia nervosa. Findings from studies of other psychiatric and neurological disorders and from animal studies demonstrate that increases in food intake and body weight can be achieved following DBS and that VNS has potential value as a means of controlling eating and inducing weight loss.

Conclusions: Neuromodulation tools have potential for reducing ED symptomatology and related behaviours, and for altering food intake and body weight. In response to such findings, and emerging neural models of ED, treatment approaches are highly unlikely to remain 'brainless'. More research is required to evaluate the potential of neuromodulation procedures for improving long-term outcomes in ED. Copyright © 2013 John Wiley & Sons, Ltd and Eating Disorders Association.

Keywords

eating disorders (ED); anorexia nervosa (AN); bulimia nervosa (BN); transcranial magnetic stimulation (TMS); transcranial direct current stimulation (tDCS); vagus nerve stimulation (VNS); deep brain stimulation (DBS)

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Introduction

Eating disorders

The eating disorders (ED) anorexia nervosa (AN), bulimia nervosa (BN), eating disorders not otherwise specified (EDNOS) and binge eating disorder (BED) are characterised by pathological eating behaviours and body image disturbance. Obesity is a heterogeneous condition that is not classified as an ED (Marcus & Wildes, 2009). However, it is both a risk factor and a consequence of ED. Moreover, a subgroup of obese people has significantly altered eating behaviour (e.g. loss of control over eating), and the combination of ED and obesity is increasing (Darby et al., 2009).

In the past decade, there has been an increase in studies of the neural underpinnings to ED. A number of systematic reviews have assessed the literature on structural imaging in ED (Van den Eynde et al., 2012) and functional neuroimaging with and without symptom provocation in AN patients (Pietrini et al., 2011; Zhu et al., 2012). In addition, there are narrative reviews on the use of neuroimaging techniques in ED (Frank, Bailer, Henry, Wagner, & Kaye, 2004; Frank & Kaye, 2012; Kaye, 2008; Kaye, Fudge, & Paulus, 2009; Kaye, Wagner, Fudge, & Paulus, 2011; Michaelides, Thanos, Volkow, & Wang, 2012). Whilst these reviews summarise findings from a variety of neuroimaging techniques including positron emission tomography and single photon emission computed tomography, the most extensive imaging data in ED arise from fMRI research.

Functional MRI has advanced our understanding of the neural differences between people with ED and their healthy counterparts. Altered activity in the insula (Kim, Ku, Lee, Lee, & Jung, 2012) and abnormalities in the processing of rewards (Avena & Bocarsly, 2012; Bohon & Stice, 2011; Brooks et al., 2011; Dichter, Damiano, & Allen, 2012; Holsen et al., 2012; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008) in addition to alterations in frontal regions have been reported (Brooks et al., 2011; Celone, Thompson-Brenner, Ross, Pratt, & Stern, 2011; Hollmann et al., 2012; Marsh et al., 2011; Uher et al., 2004), and subsequent neural models of ED have been developed (Brooks, Rask-Andersen,

Benedict, & Schioth, 2012; Kidd & Steinglass, 2012; Marsh, Steinglass, et al., 2009; Steinglass & Walsh, 2006).

Many of the brain regions that are proposed to be involved in the aetiology/symptomatology of ED involve parts of the ventral and dorsal circuits proposed in emotion regulation models. For example, Phillips, Drevets, Rauch, and Lane (2003) proposed that a ventral/limbic circuit is central to the identification of and response to emotional salient stimuli, whilst a dorsal or cognitive/executive functioning circuit is important for automatic regulation of emotional responses, selective attention and planning. This and other models of emotion regulation propose that there is 'bottom-up' emotion generation arising from subcortical, limbic neural structures and 'top-down' regulation by dorsal prefrontal cortical regions (Ochsner & Gross, 2007; Phillips et al., 2003). There is a growing consensus that ED may, at least in part, be explained by altered interactions within such circuitry(Kaye et al., 2009, 2011; Marsh, Maia, & Peterson, 2009; van Kuyck et al., 2009). Heightened 'bottom-up' mesolimbic drives may contribute to altered reward processing, for example in relation to food stimuli, and result in behaviours such as binge eating, whilst overactive 'top-down' processes involving the dorsal circuit may lead to excessive regulation and self-control, thus contributing to behaviours such as food restriction.

Despite the growing body of neuroimaging data and the emergence of neural models of ED, there is a lack of targeted treatment interventions. At present, the leading treatment for AN in adolescents is family based therapy (FBT); yet, there is still no 'gold standard' treatment for adult AN (Watson et al., 2012; Schmidt et al., 2012). In BN and BED, cognitive behaviour therapy (CBT) is considered the treatment of choice for adults and adolescents; yet, recovery rates are far from perfect (Brown & Keel, 2012; Schmidt et al., 2007). Drop-out and relapse rates in treatments for ED are high (Dejong, Broadbent, & Schmidt, 2012; Schmidt et al., 2012). Whilst existing treatments work for some, a significant number of individuals do not respond to any of the treatment options currently available.

Existing talking psychotherapies target explicit cognitive processes. They work by teaching patients to employ effortful and conscious strategies to divert attention from anxiety-provoking thoughts. There is an indubitable need for such approaches within the field. However, we suggest that on the basis of the neuroimaging research summarised herein, there is also a need for brain-directed approaches to be used as adjuncts to current interventions in order to improve outcomes. Whilst drug therapies are a form of brain-directed treatment, their value in ED is currently limited (Mitchell, Roerig, & Steffen, 2013) (however, see Maguire et al., this issue). Therefore, there is significant scope for investigations into techniques that have the ability to directly, focally and implicitly influence the subcortical processes proposed to underlie ED.

Neuromodulation

Neuromodulation procedures are emerging as techniques that can be used to stimulate or inhibit neural activity. Techniques range from relatively non-invasive procedures, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), to more invasive procedures requiring surgery, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Such techniques are advantageous compared with older brain-directed treatment approaches, such as electroconvulsive therapy (ECT), as they are non-lesional, adjustable and without severe side effects. Those investigated most widely and relevant to the current review are summarised in Table 1.

Two forms of non-invasive neuromodulatory techniques are TMS and tDCS. Primarily developed in order to investigate motor cortex excitability, TMS modulates the underlying cerebral cortex and neural activity beneath the site of stimulation via an electromagnetic field generated by a coil (Barker, Jalinous, & Freeston, 1985). Delivery of single pulse TMS enables examination of cortical excitability, whilst the delivery of multiple pulses over a short period, known as repetitive TMS (rTMS), induces longer lasting neural effects. When applied at a low frequency (<5 Hz), rTMS suppresses cortical excitability, whilst high-frequency rTMS (>5 Hz) enhances cortical excitability. Recent evidence suggests that high-frequency rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) has therapeutic efficacy in depression (Berlim, Van den Eynde, & Daskalakis, 2012; Fitzgerald et al., 2012; Lee, Blumberger, Fitzgerald, Daskalakis, & Levinson, 2012; O'Reardon et al., 2007; Tarhan, Sayar, Tan, & Kagan, 2012). As such, rTMS is approved by the FDA in the USA as a second-line treatment for depression.

Transcranial direct current stimulation applies a weak direct current from one electrode (excitatory; anode) to another (inhibitory; cathode). In comparison with rTMS, the mechanism by which tDCS works enables multiple stimulation designs. Switching the position of the electrodes enables swapping of excitation/inhibition between the right and left hemispheres. Despite this added feature and that in comparison with rTMS, it is safer, cheaper and easier to administer, tDCS has not been as widely investigated. However, interest in tDCS is increasing, having shown promising therapeutic effects in both Parkinson's disease (Benninger et al., 2010; Boggio et al., 2006; Fregni et al., 2006) and Alzheimer's disease (Ferrucci et al., 2008) and, more recently, in major depression (Ferrucci et al., 2009; Kalu, Sexton, Loo, & Ebmeier, 2012; Loo et al., 2012; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009).

Table 1 Common neuromodulation 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.
Vagus nerve stimulation (VNS)	Surgery	Electrical stimulation of vagus nerve conveyed to other areas of the brain.
Deep brain stimulation (DBS)	Surgery	Electrical pulses delivered to specific brain area central to condition.

Some forms of neuromodulation are more invasive and require surgical procedures. VNS involves the implantation of a stimulator device; the generator is placed under the clavicle in the chest and is connected to electrodes wrapped around the vagus nerve (Connor, Nixon, Nanda, & Guthikonda, 2012; Meneses et al., 2013). The vagus nerve, one of 12 cranial nerves, relays information to and from the brain to major organs including the heart, stomach and lungs. Electrical stimulation via VNS results in activation/inhibition of brainstem structures, which is then conveyed to other areas of the brain including the thalamus, frontal cortex, hypothalamus and limbic lobe (Chae et al., 2003). VNS is FDA approved for the treatment of intractable epilepsy and depression; yet, its therapeutic efficacy in depression is argued to require further substantiation in controlled settings (Martin & Martin-Sanchez, 2012).

Finally, DBS is a technique that has been used for more than 25 years to modulate dysfunctional neuro-circuitry. It involves the implantation of electrodes in a defined brain target deemed to be central to the clinical problem. Similarly to VNS, the electrodes are connected to a generator implanted in the body, which sends electrical pulses to the region. Marked improvements in the major motor symptoms of Parkinson's disease have been found after DBS typically of either the globus pallidus (GP), sub-thalamic nucleus (STN) or other thalamic targets (DeLong & Wichmann, 2012). Use of DBS now extends into psychiatric disorders for which there are neural-based aetiological models. For example, promising therapeutic effects have been reported following DBS of the subgenual cingulate gyrus or the ventral internal capsule/ventral striatum in major depression (Taghva, Malone, & Rezai, 2012), the nucleus accumbens (NuAcc) in obsessive compulsive disorder (OCD; de Koning et al., 2013; Greenberg et al., 2006) and the hypothalamus in Alzheimer's disease (Laxton et al., 2010).

Neuromodulation based approaches to eating disorders

We have systematically reviewed the effects of such neuromodulatory techniques on ED symptoms and related behaviours, for example food intake and body weight. The need for this review arises from (i) the limited efficacy of existing treatments for ED, in particular enduring AN, (ii) the growing number of neural-based models of ED, (iii) the variety of neuromodulation techniques being used in research and in clinical settings, (iv) recent studies that have applied neuromodulatory procedures in ED patients, and (v) a perceived need to help direct the field of brain-directed interventions in ED.

Methods

A systematic review was conducted, following the recommendations outlined in the PRISMA guidance. The literature search was conducted independently by two investigators and then compared. Any disagreements were resolved by further examination of the full text and via consensus. Relevant studies were identified using online databases Pubmed, PsychInfo and Web of Knowledge. Key search terms are included below in the search strategy used in Pubmed:

((brain stimulation[Title/Abstract] OR "TMS"[Title/Abstract] OR transcranial magnetic stimulation[Mesh Terms] OR "tDCS"[Title/Abstract] OR "transcranial direct current stimulation"[Title/Abstract] OR transcranial stimulation[Title/Abstract] OR vagus stimulation[Title/Abstract]) AND (food[MeSH Terms] OR food [Title/Abstract] OR eating[MeSH Terms] OR body[MeSH Terms] OR anorexia[MeSH Terms] OR anorexi*[Title/Abstract] OR bulimia[MeSH Terms] OR bulimi*[Title/Abstract] OR obesity [MeSH Terms] OR obes*[Title/Abstract] OR binge eat*[Title/Abstract]))

Searches using Web of Knowledge and PsychInfo were conducted by organising key search terms into two groups. The first group related to neuromodulation techniques, for example ("brain" AND "stimulation"), "TMS", "tDCS", ("transcranial" AND "stimulation"), "VNS" and ("vagus" AND "stimulation"), whilst the second group consisted of ED salient words including "food", "eating", "body", "anorexia", "bulimia", "obesity" and "binge eat". The first group of neuromodulation terms was crossed with each ED salient word.

Initially, all of the identified articles were screened and included on the basis of relevance to the topic via inspection of their title and abstract. Publications were then cross-referenced, published review articles were examined for additional relevant studies and experts in the field were contacted in order to source any additional relevant literature. The full text versions of the remaining articles were then assessed in more detail. An overview of the literature search is shown in Figure 1.

Inclusion/exclusion criteria

We included articles in English (and German) that explored the effects of a form of neuromodulation on eating-related outcomes, for example ED symptoms, food cravings, eating behaviours, food intake, weight and BMI. We included studies on healthy participants, people with ED, and people with other psychiatric or neurological disorders, and studies in animals. In addition to randomised control trials (RCTs), clinical studies, case series and case reports were included.

Several studies were excluded on the basis that their focus was not on changes to eating behaviours or body weight as a result of neuromodulation (e.g. motor excitability in Parkinson's disease). In other cases, studies were excluded that looked primarily at the use of neuromodulation techniques as a conditioned response rather than a neuromodulatory tool. A number of other studies were excluded as they focused on the effects of neuromodulation on bodily form/perception. Whilst this is relevant to ED, it was deemed that this fell out of the scope of the review. Finally, papers reporting on non-eating-related outcomes and safety issues in ED patients (e.g. cortisol concentrations and cardiac safety), and those using an uncommon methods of neuromodulation (e.g. pallidotomy) are not included.

Results

We identified 60 studies that met the inclusion criteria for this review. Five of these were conducted in healthy participants (HP), 6 were in bulimic or obese individuals, 6 were in AN patients, 18 were in individuals with other psychiatric or neurological disorders and 25 were animal studies. The studies that

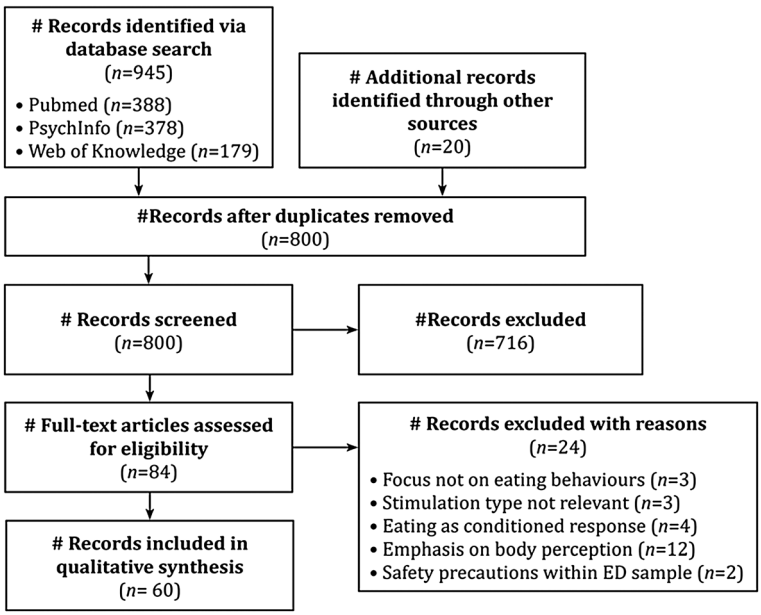

Figure 1. PRISMA flow chart of reviewed studies

were included report effects on ED symptoms, eating behaviours, food intake and changes to body weight associated with the application of neuromodulation techniques to a number of different brain regions/structures illustrated in Figure 2.

Studies in healthy participants and people with frequent food cravings

Five studies in HP were identified, with four of these using individuals who reported frequent food cravings (Table 2). The study involving a non-food craving group reported that compared with control conditions, active low-frequency (1 Hz) rTMS to the right DLPFC decreased the value assigned to food (Camus et al., 2009). Given this, it is arguable that rTMS to the right DLPFC can reduce food cravings. However, following reports of a reduction in the urge to smoke (Johann et al., 2003) and cigarette consumption (Eichhammer et al., 2003) following high-frequency (10 Hz) rTMS to the left DLPFC, two studies used a similar protocol to investigate effects on food cravings (Barth et al., 2011; Uher et al., 2005). In an RCT of 28 individuals, food cravings during exposure to food remained stable after real rTMS and increased after sham (placebo) stimulation (Uher et al., 2005). In contrast, a crossover study with an 'improved' sham condition in ten food cravers reported that real rTMS was no better than sham in reducing cravings (Barth et al., 2011).

Building on the aforementioned studies, Fregni et al. (2008) compared both tDCS protocols, anode right/cathode left and anode left/cathode right, to sham stimulation and found that food cravings reduced, remained stable or increased in these conditions, respectively. Goldman et al. (2011) compared a single tDCS condition, anode right/cathode left, to sham and found food cravings reduced in both conditions; however, the percentage change was greater following the active tDCS.

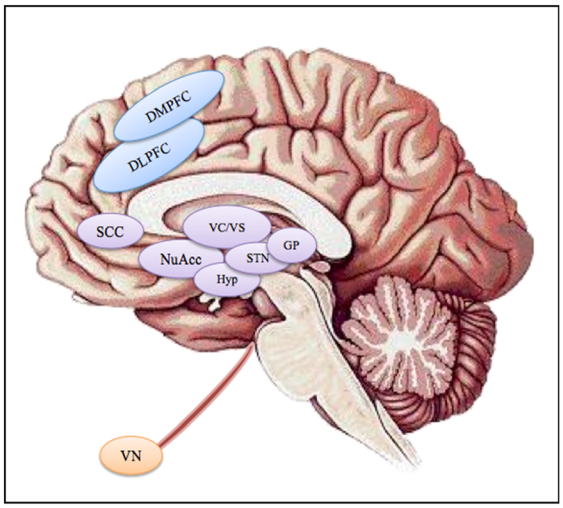

Figure 2. Brain areas targeted in reviewed studies. TMS and tDCS (blue): DMPFC, dorsomedial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex. DBS (purple): SCC, subgenual cingulate cortex; NuAcc, nucleus accumbens; VC/VS, ventral capsule/striatium; Hyp, hypothalamus; STN, sub-thalamic nucleus; GP, globus pallidus. VNS (orange): VN, vagus nerve

Studies in people with bulimia nervosa, binge eating disorder and obesity

Six studies were identified (Table 3), five of which investigated the effects of rTMS in patients with BN. Two single case studies of patients with BN and comorbid depression applied rTMS either to the left DLPFC (Hausmann et al., 2004) or both sides of the DMPFC (Downar, Sankar, Giacobbe, Woodside, & Colton, 2012).

Table 2 Studies in healthy participants and people with frequent food cravings

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Camus et al. (2009)	56	HP Right handed	rTMS	Between subjects parallel, blinded (i) real to right DLPFC, 2 controls: (ii) real to vertex and (iii) sham to right DLPFC	Right DLPFC and vertex	1 Hz, 15 minutes 50% output 900 pulses 1 session neuronavigated	Compared with control conditions, real rTMS to right DLPFC decreased the value assigned to food stimuli	
Uher et al. (2005)	28	HP Right handed Frequent food cravings	rTMS	RCT parallel, double blind (i) real versus (ii) sham	Left DLPFC	10 Hz, 20 minutes, 110% MT 1000 pulses 1 session 5 cm anterior method	Food cravings during food exposure remained stable after real rTMS and increased after sham rTMS.	
Barth et al. (2011)	10	HP Frequent food cravings	rTMS	RCT crossover, blinded (i) real versus (ii) sham	Left DLPFC	10 Hz, 15 minutes, 100% MT 3000 pulses 1 session (2 conditions) 5 cm anterior method	Real rTMS reduced cravings no better than sham.	Improved sham condition: matched to individuals' perceived pain.
Fregni et al. (2008)	23	HP Frequent food cravings	tDCS	RCT crossover, double blinded 2 active conditions: (i) anode left/cathode right and (ii) anode right/cathode left versus (iii) sham	DLPFC	2 mA, 20 minutes 1 session (3 conditions) 10–20 EEG system (F3 for left DLPFC, F4 for right DLPFC)	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.	
Goldman et al. (2011)	19	HP Frequent food cravings	tDCS	RCT crossover, blinded (i) anode right/cathode left versus (ii) sham	DLPFC	2 mA, 20 minutes 1 session (2 conditions) 10–20 EEG system (F3 for left DLPFC, F4 for right DLPFC)	Food cravings reduced in both conditions; however, percentage change was significantly greater in active tDCS. Active tDCS reduced cravings for sweet foods and carbohydrates more than sham. No difference between groups in amount of food ingested.	

Note: HP, healthy participants; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex, MT; motor threshold.

Both case studies reported complete recovery from binge/purge symptoms.

Three studies that involved larger samples (two are RCTs) applied rTMS to the left DLPFC. A therapeutic trial in 14 people with BN of 15 sessions of high-frequency, neuronavigated (guided by structural MRI scans) real/sham rTMS reported improvements in binge/purge behaviours in both groups, with no difference between conditions (Walpoth et al., 2008). In a larger sample of 38 bulimic individuals, our group found that compared with sham, a single session of real rTMS (combined with cue exposure to food) significantly reduced right-handed patients' urge to eat and binge eating episodes over the 24 h following stimulation; however, mood deteriorated in a series of left-handed participants (Van den Eynde, Broadbent, et al., 2010; Van den Eynde, Claudino, et al., 2010).

Only one study has examined neuromodulatory effects in obesity, and no study was found in BED. Montenegro et al. (2012)

Table 3 Studies in people with bulimia nervosa and obesity

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Hausmann et al. (2004)	1	BN/DP	rTMS	Case report	Left DLPFC	20 Hz, ~12 minutes, 80% MT 10 sessions; 2 per weekday for 2 weeks MRI guided	After treatment complete recovery from binge/purge symptoms and almost 50% decrease in depression scores.	
Walpoth et al. (2008)	14	BN	rTMS	RCT parallel, double blind (i) real versus (ii) sham	Left DLPFC	20 Hz, ~12 minutes, 120% MT Total of 30 000 pulses 2000 pulses p/session 15 sessions; 1 per weekday for 3 weeks MRI guided	Improvement in self-reported binge/purge behaviours, depressive and OCD symptoms in both groups. No difference between real and sham groups.	
Van den Eynde, Claudino et al. (2010)	38	BN right handed	rTMS	RCT parallel, double blind (i) real versus (ii) sham	Left DLPFC	10 Hz, 20 minutes, 110% MT 1000 pulses 1 session 5 cm anterior method	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.	
Van den Eynde, Broadbent et al. (2012)	7	BN left-handed	rTMS	Case series All received real despite being told they might receive real or sham. Compared with group in earlier study.	Left DLPFC	10 Hz, 20 minutes, 110% MT 1000 pulses 1 session 5 cm anterior method	Left-handed group: decrease in reported cravings, whilst urge to eat remained stable. Mood deteriorated in the left-handed group yet improved in the right handed group. No difference between right-handed and left-handed groups in urge to eat, urge to binge, tension or hunger.	
Downar et al. (2012)	1	BN/DP	rTMS	Case report	DMPFC (both)	10 Hz, 15 minutes, 120% MT 3000 pulses 40 sessions in total neuronavigated	(a) Full remission of binge/purge episodes and depression for more than 2 months post-treatment completion.	Full remission for 64 days. Three single binge/purge episodes due to significant psychosocial

Table 3 Continued

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
						(a) 20 sessions; 1 per weekday for 4 weeks (b) Repeat second course requested (20)	(b) After significant life stressor, requested repeat course. Remained in remission from ED and depression.	stressor leading to repeat course.
Montenegro et al. (2012)	9	OB	tDCS	RCT crossover, blinded (i) isolated sham/anodal left DLPFC or (ii) sham/anodal left DLPFC + aerobic exercise	DLPFC	2 mA, 20 minutes, 1 session (4 conditions) 10–20 EEG system (F3 for left DLPFC)	Compared with sham, active anodal left DLPFC tDCS decreased desire to eat. Anodal left tDCS combined with aerobic exercise led to greater suppression of desire to eat than tDCS/exercise alone.	

Note: DP, depression; OB, obesity; rTMS, repetitive transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; MT, motor threshold.

conducted a small crossover study of anode left/cathode right tDCS versus sham stimulation, isolated or combined with aerobic exercise in nine obese individuals. Although this used an opposing stimulation protocol to studies that have reported a reduction in food cravings (anode right/cathode left tDCS), participants' desire to eat decreased after active tDCS in comparison with sham, with a greater decrease being seen when tDCS was combined with aerobic exercise.

Studies in people with anorexia nervosa

Six studies investigating the effects of neuromodulation in patients with AN were identified (Table 4). In a case of AN with comorbid depression, 10 sessions of rTMS to the left DPLPFC were initially administered as a treatment for depression (Kamolz, Richter, Schmidtke, & Fallgatter, 2008). As improvements in both depression and AN symptoms (including weight gain) were observed, a further 31 sessions were administered along with maintenance sessions: this resulted in a continuous improvement in both the depression and AN symptoms. A pilot study by our group examined the effect of a single session of real rTMS applied to the left DLPFC in 10 cases with AN and reported a reduction in levels of feeling full, feeling fat and anxiety (Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2011).

Four studies were identified that used DBS to treat AN. Two cases of AN were treated with DBS for different comorbidities. In the first, there was complete remission of AN in a patient treated with DBS targeting the subgenual cingulate cortex (SCC) for comorbid depression (Israel, Steiger, Kolivakis, McGregor, & Sadikot, 2010). Similar reductions in AN symptoms and the maintenance of a healthy BMI were observed in another patient who underwent DBS (targeting the ventral capsule/striatum) for comorbid OCD (McLaughlin et al., 2013).

Since these promising case reports, two groups have conducted small case series' of DBS in AN. In four acutely ill adolescent AN patients, DBS to the NuAcc resulted in an average weight increase of 65% and in all patients no longer meeting diagnostic criteria for the illness (Wu et al., 2012). A recent study applied DBS to the SCC in six treatment-resistant AN patients (Lipsman et al., 2013). Nine months after DBS surgery, three patients (50%) increased and maintained their BMI greater than their historical baseline, whilst four saw improvements in AN-related obsessions, mood, anxiety and affective regulation. Along with these clinical improvements, reversals in the abnormalities seen in the anterior cingulate cortex, insula and parietal lobe were accompanied by changes in cerebral glucose metabolism.

Studies assessing eating behaviours and weight in people with other psychiatric or neurological disorders

Eighteen studies applied neuromodulation to patients with other psychiatric or neurological disorders and found concurrent changes to food cravings, eating behaviours, weight and/or BMI. Findings in patients with OCD, depression and epilepsy are presented in Table 5, followed by studies in Parkinson's disease.

In a single case report of DBS for OCD (targeting the NuAcc), the patient's weight increased by 8 kg in the first few months of treatment (Mantione, van de Brink, Schuurman, & Denys 2010). Following the initial weight increase, this patient weighed 115 kg

Table 4 Studies in people with anorexia nervosa

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Kamolz et al. (2008)	1	AN/DP	rTMS	Case report	Left DLPFC	10 Hz, 20 minutes, 110% MT 2000 pulses 41 sessions in total 10–20 EEG system (F3) (a) 10 sessions, 16 days (b) Deterioration 10 days post-treatment; second course of 6 sessions (c) Requested third course of 10 sessions (d) Maintenance therapy; 15 sessions, 2 p/week for 8 weeks	(a) Improvement in depression and ED symptoms, for example uncomplicated food intake, less negative cognitions and weight gain. (b) Reduction in depressive symptoms. (c) Significant reduction in depressive symptoms, and participation in eating programme proved to be effective after these 10 sessions. (d) Maintenance sessions administered. Continuous improvement of depression and ED symptoms.	Maintenance sessions required to reduce the chance of a second relapse.
Van den Eynde et al. (2011)	10	AN Right handed	rTMS	Case series All received real despite being told they might receive real/sham.	Left DLPFC	10 Hz, 20 minutes, 110% MT 1000 pulses 1 session 5 cm anterior method	Real rTMS resulted in reduced levels of feeling full, fat, and anxiety. Trend towards a decrease in urge to exercise. No difference in urge to restrict, urge to eat, mood, tension and hunger.	
Israel et al. (2010)	1	AN/DP	DBS	Case report	SCC Bilateral	Right-sided intermittent, 2 minutes on/1 minute off 130 Hz, 5 mA, 91 μS	Remission of ED, no relapse and maintained average BMI of 19.1. Remission from ED remained despite depressive breakthroughs.	Pharmacological treatments continued post-operatively.
Wu et al. (2012)	4	AN	DBS	Case series	NuAcc Bilateral	–	Average of 65% increase in body weight at 38 month follow-up. All patients weighed >85% of expected body weight, menstruation restored and no longer meet the AN diagnostic criteria. Depression and OCD symptoms improved.	Patients age 16–17 years, duration of illness 13–28 months. All had psychiatric comorbidities.
McLaughlin et al. (2013)	1	AN/OCD	DBS	Case report	VC/VS Bilateral	120 Hz, 7.5 V, 120 μS Monopolar	There was reduction in food/eating-related concerns. Food intake, food variety and body weight were increased. BMI maintained between 18.9 and 19.6	Symptoms worsened when cathode electrode was added.

Table 4 Continued

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Lipsman et al. (2013)	6	AN	DBS	Prospective case series	SCC	130 Hz, 5–7 V, 90 μS	At 9 months follow-up, 3 patients (50%) increased and maintained BMI greater than their historical baseline. Improvement in food/weight preoccupations, mood, anxiety, affect regulation and quality of life. Changes in cerebral glucose metabolism and reversal of abnormalities in variety brain regions.	Patients age 20–60 years, treatment resistant. Side effects include panic attacks, nausea, air embolus, pain and seizure (1 patient only).

Note: DP, depression; OCD, obsessive compulsive disorder; rTMS, repetitive transcranial magnetic stimulation; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; SCC, subgenual cingulated cortex; NuAcc, nucleus accumbens; VC/VS, ventral striatum/capsule; MT, motor threshold.

and made a conscious decision to lose weight and successfully lost 44 kg.

Three papers (relating to two studies) report effects of VNS on food cravings and weight changes in depressed patients. Compared with controls, significant changes to cravings of sweet foods (in both directions) between VNS, on/off conditions in depressed participants were reported (Bodenlos, Kose, Borckardt, Nahas, Shaw, O'Neil, & George, 2007; Bodenlos, Kose, Borckardt, Nahas, Shaw, O'Neil, Pagoto, et al., 2007). In contrast, Pardo et al. (2007) examined the effects of VNS in depressed, obese patients and found significant, effortless weight loss proportional to BMI.

Three studies of VNS in patients with epilepsy retrospectively examined changes in weight/BMI following surgery. One study reported a significant weight loss following VNS, for example in 17/27 (63%) patients (Burneo, Faught, Knowlton, Morawetz, & Kuzniecky, 2002), whilst the remaining two studies reported no significant weight change following VNS for epilepsy in both adults (Koren & Holmes, 2006) and children (Kansagra, Ataya, Lewis, Gallentine, & Mikati, 2010; Koren & Holmes, 2006).

The remaining studies report (many retrospectively) changes to eating behaviours and body weight following DBS to either the STN or GP (for the treatment of Parkinson's disease). All 11 studies report either over-eating and/or increases in cravings, weight gain and BMI following DBS (Bannier et al., 2009; Locke et al., 2011; Macia et al., 2004; Montaurier et al., 2007; Novakova et al., 2011, 2007; Sauleau et al., 2009; Strowd et al., 2010; Tuite et al., 2005; Walker et al., 2009; Zahodne et al., 2011).

Studies assessing food intake and weight in animals

Table 6 summarises the 25 animal studies that investigated the effects of neuromodulation on food intake and/or body weight. Three examined the feasibility of DBS as a potential treatment for ED, specifically AN. Lacan et al. (2008) implanted the ventromedial hypothalamus of two monkeys and reported significant increases in food intake with active high-frequency DBS compared with inactive DBS. Despite this, there was no change in body weight during the 4-month study period. The remaining two studies investigated the effects of DBS [sometimes referred to as electrical brain stimulation (EBS)] of the lateral hypothalamus (Welkenhuysen, Van Kuyck, Das, Sciot, & Nuttin, 2008) and NuAcc (van der Plasse, Schrama, van Seters, Vanderschuren, & Westenberg, 2012) in rats. The first found no significant changes to food intake, but the latter reported that DBS of the medial shell of the NuAcc (but not to the core or lateral shell) increased food intake by up to 250% (van der Plasse et al., 2012).

Eight studies examine the effects of VNS and DBS in binge eating/obesity animal models. Three RCTs demonstrate decreased food consumption and/or lowered weight gain in pigs (Sobocki, Fourtanier, Estany, & Otal, 2006; Val-Laillet, Biraben, Randuineau, & Malbert, 2010) and rats (Bugajski et al., 2007) following active VNS.

Four studies applied DBS to the hypothalamus in rats (Sani, Jobe, Smith, Kordower, & Bakay, 2007; Torres, Chabardes, & Benabid, 2012a), monkeys (Torres, Chabardes, Piallat, Devergnas, & Benabid, 2012b) and pigs (Melega, Lacan, Gorgulho, Behnke, & De Salles, 2012). High-frequency DBS to the lateral hypothalamus in rats resulted in sustained weight loss (Sani et al., 2007), whilst

Table 5 Studies assessing eating behaviours and weight in people with other psychiatric and neurological disorders

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Mantione et al. (2010)	1	OCD	DBS	Case report	NuAcc	185 Hz, 3.5 V, 90 microseconds Monopolar	First few months post-surgery weight gain of 8 kg. Then, after conscious decision to lose weight (weighing 115 kg), 10 months after dieting was at target weight of 71 kg (BMI = 25). Maintained weight at 2 years follow-up.	Simultaneous effortless smoking cessation.
Bodenlos, Kose, Borckardt, Nahas, Shaw, O'Neil, & George, 2007; Bodenlos, Kose, Borckardt, Nahas, Shaw, O'Neil, Pagoto, et al., 2007	33	DP	VNS	(a) Between groups comparison: (i) depression VNS, (ii) depression non-VNS and (iii) HC (b) Within VNS group: crossover, blinded VNS (i) on versus (ii) off	Left VN	20 Hz, 1.25 mA 0.5–84 months 1 session	Groups did not differ in mean food cravings and their ability to resist food. Between viewing food images, cravings for sweet foods differed between groups: depressed VNS had higher change scores for craving of sweets than depression non-VNS and HC.	In VNS group, cravings for sweets changed in both directions. Decrease in six participants, increase in five.
Pardo et al. (2007)	14	DP/OB	VNS		Left VN	30 Hz, 0.25–1.5 mA 250 or 500 microseconds 30 seconds on/5 minutes off 24 months	Significant, effortless weight loss proportional to initial BMI. Stimulation parameters had no effect on weight changes.	
Burneo et al. (2002)	27	EP	VNS	Retrospective	Left VN	–	Significant weight loss (>5%) in 17 patients. Remaining patients had no significant change in weight.	
Koren et al. (2006)	21	EP	VNS	Retrospective	Left VN	30 Hz, 1.25–3 mA, 500 microseconds 30 seconds on and 5 seconds off 24 months	No significant change in weight within 2 years following VNS implantation.	
Kansagra et al. (2010)	23	EP(c)	VNS	Retrospective	Left VN	–	No significant changes in BMI at 1 year and final time point (mean 4.2 years) following VNS implantation.	
Macia et al. (2004)	33	PD	DBS	Retrospective PD DBS ($n = 19$) versus PD non-DBS ($n = 14$)	STN	130 HZ, 1.5–3 V, 90 microseconds Monopolar	18/19 DBS patients had significant weight gain and increase in BMI. Significant reduction in resting EE, no change in daily EE	
Tuite et al. (2005)	27	PD	DBS	Retrospective	STN	–	Significant weight gain up to 12 months after surgery.	
Novakova et al. (2007)	25	PD	DBS	Retrospective	STN Bilateral	–	Average weight gain of 9.4 kg during first follow-up at 1–45 months post-implantation. One year later, decrease in 12 patients, increase in 6 and 3 remained stable.	

Table 5 Continued

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Montaurier et al. (2007)	23	PD	DBS	Prospective	STN	148.0 Hz, 2.7–2.8 V, 69 microseconds	Increase in body weight and fat mass after surgery. Daily EE decreased significantly.	No correlation between reduced EE and weight gain
	24	HS			Bilateral			
Walker et al. (2009)	39	PD	DBS	Retrospective	STN Unilateral	–	Compared with preoperative baseline, weight increased by mean of 4.3 kg 1 year following surgery.	
Bannier et al. (2009)	22	PD	DBS		STN		68% patients overweight/obese 3 months post-surgery, increased to 82% at 16 months post-surgery.	
Sauleau et al. (2009)	46	PD	DBS	DBS to STN ($n = 32$) versus DBS to GPi ($n = 14$)	STN/GP	130 Hz, 60 microseconds	Significantly higher increase in BMI in STN DBS patients.	
Strowd et al. (2010)	182	PD	DBS	Retrospective	STN/VMI/GP	–	Significant weight gain up to 24 months post-surgery, not predicted by stimulation target.	
Novakova et al. (2011)	27	PD	DBS		STN	–	Significant weight gain during 12 month post-implantation.	
Locke et al. (2011)	52	PD	DBS	Retrospective	STN/GP Unilateral	–	Significant weight gain following surgery, no significant difference in weight gain between GP and STN targets.	No correlation between reduced motor scores and weight gain.
Zahodne et al. (2011)	100	PD	DBS	Prospective	STN/GP	–	DBS implantation predicted over eating and an increase in cravings.	

Note: OCD, obsessive compulsive disorder; DP, depression; OB, obesity; EP, epilepsy; EP(c), children with epilepsy; PD; Parkinson's disease; DBS, deep brain stimulation; VNS, vagus nerve stimulation; NuAcc, nucleus accumbens; VN, vagus nerve; STN, sub-thalamic nucleus; GP, globus pallidous; EE, energy expenditure.

Table 6 Studies assessing food intake and weight in animals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Animal models of anorexia nervosa								
Lacan et al. (2008)	2	Monkeys	DBS	2 cycles of stimulation (a) 8 days of active, 2 days of inactive and (b) 3 days active, 3 days inactive.	vmH Bilateral	(a) 185 Hz, 2.5 V, 90 microseconds (b) 185 Hz, 3.5 V, 90 microseconds	Significant increase in food intake during active stimulation. There was no change in body weight.	
Welkenhuysen et al. (2008)	26	Rats	EBS (DBS)	(a) Acute: 4 subsequent sessions conducted in random order of amp. (b) Chronic: on/off	Lateral hypoth.	(a) 100 Hz, 0.06 millisecond, 3.5 hours, 0%, 25%, 50% and 75% amp. (b) 100 Hz, 0.06 millisecond pulses, 50% maximum amplitude	(a) Decrease in the number of wheel rotations (lower activity levels) but no impact on food intake. (b) No effect on wheel rotations or amount of food consumed.	
van der Plasse et al. (2012)	8	Rats	DBS	Comparison of DBS to 3 areas of NAcc (i) core, (ii) lateral shell (lShell) and (iii) medial shell (mShell)	NAcc	130 Hz 60 μS pulses, 200 μS off 300 μm electrodes	DBS to core had no effect on response to sucrose or food intake, to lShell reduced motivation to respond for sucrose, no effect on food intake. DBS to mShell profoundly increased food intake (250% of baseline).	Implications for medial shell of NAcc as target for DBS in AN.
Animal models of binge eating and obesity								
Sobocki et al. (2006)	8	Pigs	VNS	RCT crossover design (i) 4 weeks on versus (ii) 4 weeks off	Anterior VN	34 Hz, 4 V, 0.5 millisecond, every 3–4 hours for 24 hours	In both groups, cumulative body weight gain was lower during stimulation period compared with the control period.	Metabolic rate not affected.
Bugajski et al. (2007)	18	Rats	VNS	RCT 3 groups: (i) active VNS, (ii) inactive VNS and (iii) no VNS	Left VN Unipolar	0.05 Hz, 200 mV, 10 millisecond pulses 100 days	Significant decrease in meal size, fat weight and weight gain in VNS rats compared with controls.	
Val-Laillet et al. (2010)	8	Mini Pigs	VNS	RCT (i) real versus (ii) sham	VN	30 Hz, 2 mA, 500 μS 30 seconds on/5 minutes off 14 weeks	VNS implantation resulted in animals' weight remaining stable, decreased food consumption and decreased sweet-food cravings compared with animals with sham implants.	
Sani et al. (2007)	16	Rats	DBS	RCT (i) active continuous stimulation versus (ii) implanted inactive	Lateral hypoth.	180–200 Hz, 2.0 V, 100 millisecond pulse width, ~31 days	Significant decrease in weight gain in the stimulated compared with the non-stimulated group.	
Torres et al. (2012a)	27	Rats	DBS	Unilateral continuous, bipolar stimulation	vmH	30–130 Hz, 60 milliseconds, 222 ± 103 μA	(a) Acute HF increased food intake compared with sham.	

Table 6 Continued

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
				(a) Acute: HF (130 Hz) versus LF (30 Hz) (b) Chronic: long-term effects of HF		(a) 30 minutes (b) 16 days, 4 hours/day, 5 days/week, 3 weeks	Acute LF reduced food intake compared with sham. (b) Chronic stimulation (130 Hz) slowed down body weight intake compared with sham.	
Torres et al. (2012b)	5	MK	DBS	(a) Acute: various DBS parameters post 24 hour fasting period versus inactive (b) chronic: 8 week trial of 3 protocols	Hypoth.	(a) 30–130 Hz, 8 hours (b) 30 Hz, 80 Hz, 130 Hz continuous stimulation day/night for 8 weeks.	(a) Decreased food intake for all MK at 80 Hz (b) Significant decrease in body weight and BMI at 80 Hz. Skinfolds reduced at 80 Hz yet increased at 130 Hz. Sham MK increased their weight.	Intraventricular approach
Melega et al. (2012)	8	Mini pigs	DBS	2 groups: (i) active versus (ii) inactive	vmH Bilateral	50 Hz, 8 weeks, 507 microseconds 0.5, 1.0, 1.5 mA	All animals ate the same amount of food, yet those that received active DBS had less cumulative weight gain than non-stimulated animals.	DBS may be associated with increase in metabolic rate.
Halpern et al. (2013)	73	Mice	DBS	Randomised design (a) binge eating: surgical and non-surgical mice (b) acute DBS to NAcc] shell or dorsal striatum (c) chronic DBS in diet-induced obese mice	NuAcc shell	(a) 160 Hz, 150 μA 60 μS pulses, 1 hour (b) 160 Hz,150 μA, 60 μS pulses for 4 days	DBS to NAcc shell reduced binge eating and increased c-Fos levels in this area (measure of neuronal activity). Dopamine receptor D2 attenuated action of DBS. DBS to dorsal striatum had no influence on binge eating. Chronic DBS to obese mice reduced caloric intake and induced weight loss.	Implicates mesolimbic dopamine pathways in hedonic aspects of obesity.
Other studies in animals								
Laskiewicz et al. (2003)	60	Rats	VNS	5 conditions: (i) left vagal (0.5 Hz), (ii) both vagal nerves (0.5 Hz), (iii) left vagal (0.1 Hz), (iv) both vagal nerves in obese rats (0.1 Hz) and (v) left vagal combined with right side abdominal vagotomy	Left and right VN	0.05 and 0.1 Hz, 0.55 V, 0.1 seconds for 27 days	Body weight and total food intake decreased in all conditions. Effects of both vagal nerves stimulation on final body weight and food intake significantly more effective than only one single nerve.	
Ziomber et al. (2009)	78	Rats	VNS	3 conditions (i) active in the magnetic field exposure (MFE), versus 2 control groups with inactive solenoid without electrodes,	Left VN	0.1, 0.2, 0.5 and 1.0 Hz 50, 100, 150 and 200 mV Stimulation changed every 3 days for 15 days	Rats with solenoid electrodes significantly decreased their food intake, weight gain and serum leptin concentrations when compared with controls.	

				(ii) in the MFE and (iii) outside the MFE				
Gil et al. (2011)	24	Rats	VNS	Randomised into 3 groups: (i) active, (ii) inactive and (iii) non-operated controls	Left VN	10 Hz, 200 mV, 10 milliseconds 12 hours/day, 42 days	Active VNS stimulation reduced daily and total food intake, body weight and body fat compared with both inactive and control group. No difference in food intake or body fat between inactive and control condition.	
Banni et al. (2012)	10	Rats	VNS	2 naïve, 4 sham, 4 VNS rats compared across (a) acute (3 hours) and (b) chronic (4 weeks)	Left VN	30 Hz, 1.50 mA 30 seconds on/5 minutes off	Compared with sham, chronic VNS reduced food intake, body weight gain and amount of adipose tissue.	
Delgado et al. (1953)	6	Cats	DBS	(a) Control period 1–2 weeks before implantation versus (b) bipolar stimulation	Lateral hypoth.	60 Hz, 0.2 microsecond, 1–5 V 0.5 s, every 5 seconds, 1 hour 5–10 days	Daily stimulation produced increase in food intake.	
Stephan et al. (1971)	14	Rats	EBS (DBS)	On versus off stimulation	Lateral hypoth.	10–60 μA, 0.5 minute on/1 minute off 20 trials	50% of rats displayed stimulation bound eating.	Emphasis on copulation behaviours.
Mogenson et al. (1971)	75	Rats	EBS (DBS)	–	Lateral hypoth.	60 Hz, 6–30 μA, 5 seconds on/15 seconds off, 30 minutes	Stimulation of the lateral hypothalamic area induced feeding and/or drinking in 30 rats.	
Schallert et al. (1977)	38	Rats	EBS (DBS)	Food and water deprivation versus brain stimulation	Lateral hypoth.	100 Hz, 30–90 μA,0.2 millisecond, 1 minute on/30 seconds off	Rats not attracted to food stimuli when undeprived, nor with stimulation alone. When deprived from food/water and stimulated became attracted to food stimuli.	
Halperin et al. (1983)	8	Rats	EBS (DBS)	4 conditions: (i) saline, inactive EBS, (ii) adrenergic, inactive EBS, (iii) saline, active EBS and (iv) adrenergic, active EBS	Left lateral hypoth.	60 Hz, 14–104 μA 30 seconds on/30 seconds off, 20 trials	With combined adrenergic and EBS, food intake was significantly greater than either condition alone.	
Brown et al. (1984)	6	Dogs	DBS	RCT (i) vmH on/off versus (ii) subcortical white matter (control)	vmH white matter (control)	50 Hz, 100 μA,3.5 V 1.0 millisecond (a) deprived food for 24 hours, DBS for 1 hour, repeated with inactive, (b) 1 hour of DBS every 12 hours for 3 days	(a) Dogs receiving DBS delayed their next meal despite food deprivation, whereas non-stimulated dogs resumed eating immediately. Control subcortical white matter controls resumed eating immediately in both on/off DBS. (b) vmH DBS decreased average daily food and water intake. No influence with DBS to subcortical white matter.	
Stenger et al. (1991)	10	Rats	DBS	3 conditions: (i) vmH stimulated, (ii) extra vmH stimulated and (iii) vmH implanted controls	vmH	50 Hz, 300 μA, 100 microseconds 20 trains of 60 seconds, 400 milliseconds on/600 milliseconds off, 12 sessions	Significant reduction in weight gain in vmH stimulated group compared with both controls.	

Table 6 Continued

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Bielajew et al. (1994)	49	Rats	EBS (DBS)	2 conditions: (i) vmH and (ii) adjacent areas of vmH	vmH	50 Hz, 300 μA, 20 trains of 60 seconds 400 milliseconds on/600 milliseconds off, 3 hour duration × 3 sessions	Stimulation bound activity associated with decrease in weight gain and food intake. Weight gain and food intake not affected by electrode placement.	
Ruffin et al. (1999)	8	Rats	EBS (DBS)	RCT crossover design: (i) active versus (ii) sham	vmH	20–25 μA, 1 millisecond pulse, 9 millisecond interval 30 seconds on/30 seconds off, 15 minutes	vmH suppressed feeding and increased metabolism. No change with sham.	
Lehmkuhle et al. (2010)	35	Rats	DBS	(i) chronic stimulation versus (ii) 4 control groups	vmH	150 or 500 Hz 10 μA, 250 microsecond pulses 6 weeks	Stimulated animals gained weight at a lower rate than controls. No significant difference in food intake between groups.	Weight gain altered without affecting feeding behaviours.

Note: EBS/DBS, electrical/deep brain stimulation; VNS, vagus nerve stimulation; vmH, ventromedial hypothalamus; NuAcc, nucleus accumbens; VN, vagus nerve; VMH, ventromedial hypothalamus; MT, motor threshold.

DBS to the ventromedial hypothalamus produced mixed findings. Torres, Chabardes, and Benabid (2012a) found that compared with inactive DBS, high-frequency (130 Hz) DBS increased food intake, whilst low-frequency (30 Hz) DBS reduced food intake in 27 rats. In contrast, Torres, Chabardes, Piallat, et al. (2012b) found that 8 hours of high-frequency (80 Hz) DBS decreased food intake in all five monkeys after fasting and reduced body weight/BMI in three (of four) monkeys after 8 weeks of stimulation. Melega et al. (2012) administered low-frequency DBS to the ventromedial hypothalamus in eight mini pigs given double their amount of daily food for a 2-month period. All animals consumed the food given; however, those who received active DBS showed lower cumulative weight gain than the non-stimulated group.

As far as we are aware, only one animal study has investigated the effects of DBS on binge eating behaviours. Halpern et al. (2013) demonstrated that short-term (1 hour) DBS to the NuAcc (but not the dorsal striatum) reduced binge eating in mice, and chronic stimulation to the NuAcc over 4 days led to a reduction in caloric intake and induced weight loss.

Four studies report changes in food intake and/or body weight in rats following VNS. These studies applied VNS for a period of 15–42 days. All four found a reduction in food intake, body weight/fat and/or weight gain following VNS (Banni et al., 2012; Gil, Bugajski, & Thor, 2011; Laskiewicz et al., 2003; Ziomber et al., 2009).

Finally, 10 studies suggest changes in food intake and weight as a result of DBS to two areas of the hypothalamus. In general, stimulation of the lateral hypothalamus induced food intake in both cats and rats (Delgado & Anand, 1953; Halperin, Gatchalian, Adachi, Carter, & Leibowitz, 1983; Mogenson, 1971; Schallert, 1977; Stephan, Valenstein, & Zucker, 1971). However, a number employed complex protocols involving comparisons with copulatory behaviours (Stephan et al., 1971) or DBS/EBS in conjunction with food deprivation (Schallert, 1977) or adrenergic interventions (Halperin et al., 1983), so their findings lack comparability. DBS/EBS to the ventromedial hypothalamus consistently reduced food intake and/or reduced weight gain (Bielajew, Stenger, & Schindler, 1994; Brown, Fessler, Rachlin, & Mullan, 1984; Lehmkuhle, Mayes, & Kipke, 2010; Ruffin & Nicolaidis, 1999; Stenger, Fournier & Bielajew, 1991).

Discussion

This review provides evidence that neuromodulation has potential for altering disordered eating behaviours, food intake and body weight. Non-invasive neuromodulation techniques (rTMS and tDCS) have been shown to prevent and reduce cravings in individuals who report frequent food cravings, and rTMS applied to the prefrontal cortex also has shown promise for reducing BN symptoms. In AN, the data also demonstrate potential for symptom improvement including weight gain, following both rTMS and DBS. Furthermore, reports of significant weight gain following DBS for Parkinson's disease provide grounds for investigating the use of DBS in AN, whilst VNS may have potential as an alternative bariatric intervention.

Methodological considerations

Findings reported in this review must be interpreted in the context of the varying methodologies considered. Four different techniques, rTMS, tDCS, VNS and DBS, have been reviewed, and within each exists the potential for a wide range of protocols.

Each technique has the ability to suppress/enhance neural activity via a number of different parameters—frequency, duration, intensity, number of pulses, number of sessions and stimulation sites. Such differences may help explain why some studies report no changes in ED symptoms or weight following neuromodulation (Barth et al., 2011; Kansagra et al., 2010; Koren & Holmes, 2006; Walpoth et al., 2008). The degree to which studies vary from one another methodologically also limits their comparability and hence the generalisability of these findings. On the other hand, the number of neuromodulatory techniques available and the wide range of protocol options possible within each means that the field is advancing along a broad front.

Further studies on the neural effects of neuromodulation are needed to optimise protocols: these are likely to arise from research involving online neuroimaging/neuromodulation. Data from animal models are also important but must be interpreted with caution, as factors such as the ratio of neuromodulation device (e.g. TMS coil size) to head size, coil orientation, anaesthesia and mechanical restraint are just a few elements that need to be considered when findings are extrapolated to humans (Vahabzadeh-Hagh, Muller, Gersner, Zangen, & Rotenberg, 2012). Finally, although limited by issues of stimulation focality and differences between animal and human brains, animal models are likely to provide important information on the mechanisms of neuromodulation and their potential for use in the treatment of disorders such as ED.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation has been investigated in healthy individuals, in those reporting frequent food cravings, and in patients with BN and AN. Most of this work has involved high-frequency (excitatory) rTMS to the left PFC. The studies demonstrate its promise in stabilising food cravings during food exposure and reducing both BN and AN symptoms. Arguably, this may result from restoring altered 'top-down' cognitive control in relation to emotional and other self-regulation processes. Given the demonstrated ability of rTMS to modulate food cravings and binge eating episodes, in addition to its non-invasive, safe and relatively tolerable nature, it is perhaps surprising that no studies have investigated its potential in BED or obesity. Lastly, given the chronic and life-threatening nature of AN and the promising data on rTMS in AN, larger, sham-controlled studies are needed.

Use of brain imaging techniques in ED is likely to increase knowledge of the neural correlates of disordered eating, and this will enable refinement and optimisation of rTMS protocols for treating specific ED. In particular, the role of right fronto-temporal circuits in ED as outlined in a review of brain lesions in ED (Uher & Treasure, 2005) and reports of ED resolution following right temporal lobe injuries (Levine, Lipson, & Devinsky, 2003) suggest that right-sided rTMS may be equally, if not more, effective than the predominately left-sided rTMS protocols.

Transcranial direct current stimulation

Increased knowledge on the role of hemispheric lateralisation in ED, together with improvements in the design of neuromodulation protocols, is likely to emerge from studies involving tDCS. To date, most tDCS research has been in relation to food cravings and has shown that excitation of the right/inhibition of the left PFC reduces cravings during cue exposure. Stabilisation of cravings during exposure was observed with the opposite tDCS protocol, which is somewhat consistent with the rTMS literature. The idea that increasing activity in the right PFC may decrease cravings/appetite and re-establish control over eating is also consistent with the right brain hypothesis of obesity (Alonso-Alonso & Pascual-Leone, 2007). It is possible that there is some type of inter-hemispheric imbalance in conditions involving cravings and over eating, but more neuroimaging-based evidence is required.

In comparison, the idea of right hemispheric dominance in AN, specifically hyperactivity in the right frontal regions, is somewhat established, and it is possible that anodal left/cathodal right tDCS may aid in altering/resetting inter-hemispheric balance (Hecht, 2010). This is consistent with the TMS literature in AN, which shows symptom reduction following excitation of the left DLPFC. By comparing the two possible tDCS designs to sham tDCS in AN, the possible role of hemispheric lateralisation in the illness may be elucidated. As in the case of rTMS, there is a need for more investigations of tDCS within ED populations.

Vagus nerve stimulation

Evidence from the use of VNS in other psychiatric and neurological disorders and in animal studies supports the argument for more investigations in ED, including obesity. Whilst VNS seems to have induced weight loss in a proportion of participants with depression, obesity or epilepsy, VNS in animals has consistently been associated with reductions in food intake and/or weight loss.

The vagus nerve is the major neural pathway carrying information to the gastrointestinal tract. In the current review, VNS has been associated with changes in food intake and resulting body weight, suggesting that vagal stimulation mediates satiety signals. Given the increasing prevalence, high morbidity and mortality of obesity, VNS has potential as an alternative to more invasive treatments for morbid obesity, which are often associated with severe side effects and unsustainable weight loss.

Deep brain stimulation

Deep brain stimulation has been used in a number of treatment studies of AN, in part as a result of emerging neural-based models of AN. The results are promising—two case reports resulting in remission of the illness, and two case series resulting in increases in body weight and reductions in symptoms in most patients. Furthermore, the reviewed cases have demonstrated DBS to be a safe procedure with minor side effects. Existing studies of DBS in AN have targeted a variety of different brain structures, and thus, more research is needed in order to establish optimal DBS targets. Moreover, larger controlled trials are needed to establish the long-term efficacy of DBS in this difficult to treat population.

Weight gain following DBS for Parkinson's disease has implications for the use of DBS in AN. Although the reduction in motor activity (e.g. tremors) as a result of DBS may contribute to resulting weight gain, two studies found no correlation between weight gain and reduced motor activity following DBS (Locke et al., 2011; Montaurier et al., 2007). A number of explanations have been proposed including the suggestion that the DBS current may spread to the hypothalamic satiety centres. In support of this, a number of animal studies report increases in food intake and/or body weight following DBS to the lateral hypothalamus. In contrast, stimulation

to the ventromedial hypothalamus shows the opposite, particularly when applied at lower frequencies. Interestingly, two studies showed lower rates of weight gain in stimulated animals despite no changes in the amount of food consumed, suggesting that DBS may alter metabolic rate (Lehmkuhle et al., 2010; Melega et al., 2012).

Considerations for neuromodulation in eating disorders

Eating disorders are complex, multifaceted mental illnesses, associated with altered thinking and beliefs, heightened fear and anxiety responses, mood disturbances and a myriad of other symptoms. The ED are therefore not simply about eating. Although this review reports solely on the effects of neuromodulation on eating-related behaviours and resulting weight gain/loss, such changes are likely to arise as a result of effects to some of the underlying cognitive, emotional and self-regulatory aspects of ED, such as cognitive rigidity, impaired decision making, poor inhibition and altered self-control. Such traits are proposed to be caused by the same dysfunctional fronto-subcortical circuits (Celone et al., 2011; Marsh et al., 2011; Marsh, Steinglass, et al., 2009; Sato et al., 2013). Neuromodulation is likely to alter such neurocognitive impairments in ED; however, further investigations employing neuropsychological outcomes are required.

Changes in neuropsychological aspects of ED following neuromodulation may also result from alterations associated with neuroplasticity. Studies in animals have demonstrated that repeated sessions of high-frequency rTMS induce long-lasting effects in neuroplasticity (Gersner, Kravetz, Feil, Pell, & Zangen, 2011). Such findings have implications for intractable, neurocircuit disorders such as AN. Changes in neuroplasticity highlight the potential of including exposure therapies with neuromodulation protocols in ED, to facilitate extinction learning (Koskina, Campbell, & Schmidt, 2013). In rats, high-frequency TMS paired with exposure to a conditioned stimulus facilitated fear extinction up to 24 hours post-stimulation (Baek, Chae, & Jeong, 2012). Whilst a number of studies reviewed here include exposure to highly palatable foods immediately before and after neuromodulation, online approaches applying neuromodulation during exposure tasks may improve outcomes.

Similarly, individual differences in cortical plasticity have been shown to modulate the behavioural effect of neuromodulation (Plewnia et al., 2013). Research into individual neural patterns will enable more precise, personalised protocols for rTMS, tDCS, VNS and DBS. Altering neuromodulation parameters such as stimulation site and frequency (excitatory/inhibitory) as a result of a better understanding of hemisphere lateralisation and hyperactivity or hypoactivity of certain brain regions is one likely possibility. In addition, brain imaging could be used to identify biomarkers of treatment response and thus individualised neuromodulation foci.

Such neural targets may include the insula and other subcortical structures involved in emotional responses and reward processing, and implicated in brain imaging ED research. However, the neural effects of common non-invasive neuromodulation techniques such as rTMS and tDCS are thought to be limited to the outer cerebral cortex. Continuing innovation within the neuromodulation domain has led to the development of tools with both improved focality and a greater depth of modulatory effects. Deep TMS operates on the same principle of electromagnetic induction as standard TMS. However, the standard TMS figure-of-eight coil alters cortical excitability up to a depth of 1.5–2.5 cm. In comparison, the most widely used and safety-tested deep TMS coil—the H-coil—exerts neuromodulatory effects up to 6 cm from the scalp (Bersani et al., 2013; Zangen, Roth, Voller, & Hallett, 2005). Early evidence suggests that patients with treatment-resistant depression who are also ECT non-responders may benefit from deep TMS (Rosenberg, Zangen, Stryjer, Kotler, & Dannon, 2010). Deep TMS may therefore have a place in future ED neuromodulation applications. Modulation of both the cerebral cortex and limbic neural circuits that deep TMS may induce could enable changes to both the dysfunctional 'top-down' dorsal circuits as well as the 'bottom-up' ventral systems proposed to underlie ED. Similarly, building on advances from TMS research, magnetic seizure therapy (MST) induces a seizure via high-frequency TMS. Despite the same final outcome as ECT, that is, a 'therapeutic' seizure—increased stimulation focality, lessened side effects in conjunction with similar antidepressant response rates to ECT have been found in the early stage of MST investigations, indicating that this a preferable alternative (Hoy et al., 2013).

Conclusions

Increasing knowledge of the neural underpinnings of ED, and the evidence emerging from neuromodulation studies, indicates that treatments for ED will not remain 'brainless'. Although neuromodulation treatments are unlikely to be stand-alone treatments for ED or obesity, this review demonstrates the potential of rTMS, tDCS, VNS or DBS to improve outcomes when coupled with current therapeutic interventions. In particular, reducing problematic eating behaviours and promoting weight gain in enduring and chronic cases of AN seem feasible via the use of neuromodulation techniques.

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