Current Diabetes Reports (2019) 19:152
https://doi.org/10.1007/s11892-019-1250-2

OBESITY (KM GADDE, SECTION EDITOR)

Brain Stimulation to Modulate Food Intake and Eating Behavior

Rebecca Dendy[1] · Emma J. Stinson[2] · Nicolas Guerithault[3] · Marci E. Gluck[1]

Abstract

Purpose of Review Appetitive behaviors are mediated through homeostatic and reward signaling of brain circuits. There has been increasing interest in the use of neuromodulation techniques aimed at targeting brain regions such as the lateral prefrontal and subcortical regions associated with dysregulation of eating behaviors.

Recent Findings Invasive brain stimulation techniques have demonstrated promising results in treating severe and enduring anorexia nervosa and morbid obesity. In addition, non-invasive techniques have been shown to successfully reduce food craving, hunger ratings, and calorie intake as well as binge/purge symptoms in eating disorders.

Summary Brain stimulation offers promising results for treating symptoms associated with eating disorders and modifying appetitive behaviors including craving and caloric consumption. Future research should focus on identifying optimal frequency and duration of stimulation and employ longitudinal studies to assess long-term effectiveness on clinical outcomes such as eating disorder symptomatology, weight loss, and sustained improvements in eating behaviors over time.

Keywords Neuromodulation · Obesity · Eating disorders · Prefrontal cortex · tDCS · dlPFC

Abbreviations

tDCS	Transcranial direct current stimulation
AN	Anorexia nervosa
BN	Bulimia nervosa
BED	Binge eating disorder
dlPFC	Dorsolateral prefrontal cortex
DBS	Deep brain stimulation
VNS	Vagus nerve stimulation
TMS	Transcranial magnetic stimulation
rTMS	Repetitive transcranial magnetic stimulation
NAc	Nucleus accumbens
NIBS	Non-invasive brain stimulation
dmPFC	Dorsomedial prefrontal cortex
SCC	Subcallosal cingulate
cTBS	Continuous theta burst stimulation

This article is part of the Topical Collection on *Obesity*

✉ Marci E. Gluck
gmarci@niddk.nih.gov

Rebecca Dendy
dendyrg@gmail.com

Emma J. Stinson
emmstinson@gmail.com

Nicolas Guerithault
guerithaultnicolas@gmail.com

[1] Obesity and Diabetes Clinical Research Section, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 4212 North 16th Street, Room 541, Phoenix, AZ 85016, USA

[2] Department of Epidemiology & Biostatistics, Drexel University, Philadelphia, PA, USA

[3] Arizona State University, Tempe, AZ, USA

Introduction

There are a number of brain regions involved in regulating the homeostatic and hedonic aspects of eating behavior. Hypothalamic nuclei are integral for maintaining energy homeostasis, while limbic and cortical structures are involved in the non-homeostatic pursuit of food for the sake of reward and pleasure [1]. Irregularities in neural activity within homeostatic or reward circuits may play a role in dysregulated eating behavior, including those which contribute to the development of obesity and eating disorders such as anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). Obesity is a growing health problem in the USA and is a major risk factor for several chronic diseases including heart disease, stroke, type 2 diabetes, and certain forms of

Published online: 02 December 2019

cancer. There is evidence that certain forms of addiction and the food cravings that are present in obesity share similar underlying mechanisms, such as dysregulation of dopaminergic activity in mesolimbic pathways [1–4]. Research on the pathogenesis of AN and BN has also investigated the dysregulation of non-homeostatic reward pathways as a causal mechanism for the development of eating disorders [5].

The dorsolateral prefrontal cortex (dlPFC) has been identified as a key brain region involved in the regulation of eating behaviors, and plays a critical role in aspects of executive function such as inhibitory control [6, 7], the integration of reward signals, and the planning and execution of goal-directed behaviors [3]. Associations have been observed between obesity and decreased functional activity in lateral regions of the prefrontal cortex following a meal [8••, 9, 10], elucidating a potential mechanism contributing to the development of obesity through dysregulation of eating behaviors. This executive dysfunction may also worsen as a consequence of obesity, creating a negative feedback loop that may make it progressively more difficult for obese individuals to change their eating behaviors [11••].

Appetitive behaviors are complex and mediated through homeostatic and reward signaling of brain circuits. Thus, there has been increasing interest in the development of treatments aimed at targeting brain regions associated with appetite behaviors such as lateral prefrontal and subcortical regions. Neuromodulation is one such technique, as it alters the electrical or chemical activity in the nervous system through various means to improve certain biological functions [11••] and can either stimulate or inhibit central or peripheral autonomic nervous processes to influence homeostatic and reward pathways associated with food intake. These techniques may be either invasive, such as deep brain stimulation (DBS) and vagus nerve stimulation (VNS), or noninvasive, such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). This review will provide an overview of the use of these four neuromodulation techniques in the context of regulating homeostatic and reward-based pathways associated with food craving and consumption.

Invasive Techniques

Deep Brain Stimulation

DBS is an invasive procedure whereby electrodes are surgically implanted in order to stimulate a target brain region of interest [12, 13]. DBS is currently approved by the US Food and Drug Administration (FDA) for the treatment of essential tremor, Parkinson's disease, dystonia, epilepsy, and treatment-resistant obsessive-compulsive disorder, under a humanitarian device exemption. While other non-invasive forms of stimulation such as rTMS or tDCS are unable to penetrate to regions deep below the cortex, DBS allows for direct stimulation of deeper regions such as the hypothalamus and the nucleus accumbens (NAc). These regions are central to energy homeostasis and reward processing, respectively, and are thus popular target regions for DBS in influencing appetitive behavior [12]. Historically, adverse risks of DBS include intracranial hemorrhage, ischemic stroke, seizure, and venous air embolus [14]. However, given improvements in safety over recent years, the procedure may be a consideration for individuals suffering from severe forms of obesity or eating disorders, who have failed to benefit from non-invasive therapies [15].

Potential applications of DBS for the treatment of obesity have focused on the lateral hypothalamus (LH) and the ventromedial nucleus of the hypothalamus (VMN), two regions that are critical for appetitive and satiety homeostatic signaling, respectively [12]. In rodents, stimulation of the VMN typically leads to appetite restriction and weight loss [16, 17]. A pilot study using DBS to bilaterally target the LH in humans with intractable, severe obesity resulted in an increased resting metabolic rate, with significant reductions in weight in two of the three subjects, and no adverse events reported after 2.5 years of follow-up [18]. Another case study demonstrated the potential usefulness of DBS for one woman with severe obesity and treatment-resistant depression by targeting the NAc, resulting in substantial weight loss [19].

Eating disorders have also been associated with dysregulated reward processing, including altered activity in regions such as the NAc [5]. There is evidence that DBS targeted to the NAc may help promote weight gain in individuals with intractable AN [20]. Similarly, one study suggested successful use of DBS in 16 women with treatment-resistant AN by targeting the subcallosal cingulate (SCC) [21], a region with important network connections to cortical and limbic structures [22]. Human studies on the usefulness of DBS for treatment of BN or BED are lacking, as this type of invasive treatment is not warranted, and less invasive stimulation techniques such as rTMS or tDCS are preferable.

Vagus Nerve Stimulation

The vagus nerve runs from the brain throughout the body, connecting to organs involved in digestion including the esophagus, stomach, intestines, liver, and pancreas [23, 24]. It plays a primary role in food intake in the short term, but secondary to its role in satiety signaling, there is evidence for longer-term effects [24], including changing eating habits and stimulating weight loss [23]. VNS operates through a pulse generator implanted in the left upper chest with an electrode lead wire attached to the left mid-cervical vagus nerve through a second incision in the left neck [25]. It is FDA approved for treating epilepsy and depression and more recently has been

explored as a potential treatment for obesity. Vagus nerve signaling is reduced in obesity, resulting in decreased satiety. It has been reported that VNS has the potential to benefit individuals with obesity by increasing this signaling pathway and subsequently increasing satiety [24, 26••], although the effects of VNS on food intake are equivocal. In one study of patients being treated for epilepsy or depression utilizing a VNS device, caloric intake was reduced in lean individuals when the VNS device was turned on but no effect was observed in individuals with obesity [27]. In a small study conducted in individuals with Prader-Willi Syndrome ($n = 3$), a genetic disorder characterized by hyperphagia, one patient had a slow decline in body weight and two patients had no changes following VNS [28]. The current literature indicates variability in the methods, frequency, location, duration of stimulation, and differences in the electrode designs themselves which may explain the mixed results of VNS on weight loss in humans [24]. In contrast to VNS, vagal nerve blocking (vBloc) therapy has been studied well and is currently FDA approved for long-term treatment of obesity. Unlike the VNS therapy, vBloc is a laparoscopic intraabdominal procedure in which electrodes are placed on the dissected anterior and posterior vagus nerve trunks at the gastroesophageal junction, and low-energy, high-frequency electrical pulses are sent via a rechargeable neuroregulator placed in a subcutaneous pocket on the side of the chest. Although the precise mechanism of vBloc in promoting weight loss is not known, it is believed that blockade of both the afferent and the efferent vagal signals results in changes in hunger and satiety. In an RCT of 239 subjects with class II or III obesity, active vBloc therapy led to an average weight loss of 9.2% vs. 6.0% with a sham device at 12 months [29]. Another 12-month sham-controlled RCT failed to show superiority for the vBloc therapy [30]. In summary, VNS has potential utility for weight loss in patients with obesity, but it has not been studied well to date. In contrast, vBloc has been studied in large RCTs and showed limited efficacy.

Non-invasive Techniques (see Tables 1 and 2)

Repetitive Transcranial Magnetic Stimulation

rTMS is a form of non-invasive brain stimulation (NIBS), a popular method of modulating cortical areas such as the dlPFC [31]. Repeated electromagnetic pulses are administered through a coil to a specified brain region at a frequency between 1 Hz and 20 Hz [32]. Whether the modulation stimulates or inhibits cortical excitability depends on the pulse frequency, with high frequencies increasing activity in the specified region and lower frequencies inhibiting activity [32]. Although rTMS is considered safe, patients have commonly reported uncomfortable side effects including mild headaches, pain at the stimulation site, neck pain, and dizziness. Rare but more serious side effects have occurred, including syncopal vagal episodes, mania, and seizures during sessions [33, 34].

Several studies have shown that high-frequency rTMS applied to the dlPFC effectively reduced not only subjective craving for cigarettes [35] and cocaine [36] but also cigarette use in active smokers [37]. There is a growing body of literature indicating shared common neurobiological substrates of food and drug cravings [38, 39••], suggesting a potential role for non-invasive brain stimulation in controlling appetitive behavior. In the first study of rTMS to target eating-related behavior, Uher and colleagues [40] found that a single active stimulation, compared with sham stimulation, of the left dlPFC mitigated an increase in food craving after exposure to rewarding foods, although snack food consumption within 5 min after stimulation did not differ between the treatment groups (Fig. 1). However, another group failed to observe differences in self-reported cravings between sham vs. active treatment groups in healthy women who endorsed frequent food cravings [41]. Findings from these studies prompted more recent investigations examining the potential therapeutic effects of high-frequency rTMS in patients with eating disorders [42–47, 48••].

In patients with BN, researchers have observed a range of changes in eating disorder symptoms including complete cessation of binge/purge episodes [43], a reduction in binge/purge episodes and decreased self-reported urges to eat [42], whereas another study found no differences at all in binge/purge behaviors between active and sham groups [44]. Similarly, in studies of individuals with AN, rTMS has been shown to reduce levels of core anorexia symptoms [46, 47], improve mood scores [47, 48••], and decrease interest in purging behavior [46], although one study demonstrated only modest evidence of symptom reduction [48••].

A recent study of continuous theta burst stimulation (cTBS), used to inhibit cortical activity to the left dlPFC, revealed a significant effect of increased consumption of calorie-dense foods, but not for less rewarding low-calorie foods, in the active cTBS group compared with sham cTBS [49]. This finding offers further support that the role of the dlPFC on food intake relates to food reward and is perhaps less involved with any homeostatic feedback regarding energy balance.

Transcranial Direct Current Stimulation

Another popular method of NIBS is tDCS, which modulates cortical and subcortical excitability by delivering electrical current across the skull via 2 electrodes that are placed on the scalp at the targeted brain region [50]. The anode, the active electrode, delivers the flow of current into the brain, inducing neuronal depolarization which leads to increased spontaneous firing in

Table 1 NIBS: studies and sample characteristics

First author, year	Within/ between	Cr/Con/ both	*N*	Population	Age	BMI	Sex (%F)	Time since last meal	Intervention	Intersession interval	Outcome measure CR	Outcome measure CON
Barth, 2011 [41]	W	Cr	10	H; FC	28.3	27.8	100	3 h	rTMS	7 days	VAS	NA
Fregni, 2008 [57]	W	Both	21	H; FC	23.7	–	–	3 h	a-tDCS	48 h	VAS	Calories consumed
Gluck, 2015 [62•]	B	Con	9	Obese	42	38	66.7	Morning fast	a-tDCS, c-tDCS	NA	NA	% WMEN consumed
Goldman, 2011 [56]	W	Both	19	H; FC	32.5	27.3	68.4	4 h	a-tDCS	48–72 h	VAS	% change in the decrease of food consumed
Jauch-Chara, 2014 [61]	W	Con	14	H	24.8	22.7	0	6 h	a-tDCS	14 days	NA	Calories consumed
Kekic, 2014 [55]	W	Both	20	H; FC	26.4	23.9	100	Not specified	a-tDCS	≥ 48 h	FCQ-S	Percentage consumed
Lapenta, 2014 [6]	W	Both	9	H; FC	23.4	21.9	100	3 h	a-tDCS	7 days	VAS	Calories consumed
Lowe, 2014 [49]	W	Both	21	H; FC	21.1	23.4	100	3 h	cTBS	7 days	FCQ-S	Amount consumed (grams)
Montenegro, 2012 [59]	W	Cr	9	Overweight-obese	24	28.2	44.4	2–3 h	a-tDCS	48–120	VAS	NA
Uher, 2005 [40]	B	Both	28	H; FC	25.2 active; 26.4 sham	24.7 active; 23.3 sham	100	≥ 3 h	rTMS	NA	VAS	Calories consumed
Van den Eynde, 2010 [42]	B	Cr	37	BN or EDNOS-BN	30.5 active; 29.5 sham	25.8 active; 25.0 sham	78.6 active; 88.9 sham	2 h	rTMS	NA	VAS	NA
Kekic, unpublished data [64]	W	Cr	38	B	25.85	21.65	94.87	Not specified	a-tDCS	≥ 48 h	VAS	NA

a-tDCS, anodal tDCS; *c-tDCS*, cathodal tDCS; *cTBS*, continuous theta burst stimulation; *Cr*, craving; *Con*, consumption; *NBIS*, non-invasive brain stimulation; *VAS*, visual analog scale; *FCQ-S*, Food Craving Questionnaire-State; *WMEN*, weight-maintaining energy needs; *H*, healthy; *FC*, food cravers (i.e., participants that reported strong and frequent food cravings for the experimental foods); *BN*, patients with bulimia; *EDNOS-BN*, patients with an eating disorder not otherwise specified–bulimic type

[a] Fregni was excluded from the craving analysis due to insufficient data to calculate an effect size

[b] Gluck was excluded from the meta-analysis because acute dietary outcomes were not measured

[c] Kekic was excluded from the consumption analysis due to insufficient data to calculate an effect size

(From: Lowe CJ, et al. Psychosomatic Medicine;79:2–13, with permission from Wolters Kluwer Health, Inc.) [64]

Table 2 NIBS: stimulation parameters employed

		rTMS-specific parameter				tDCS-specific parameters						
			Electrode placement									
First Author, Year	Intervention	Coil Placement	% MT	Frequency (Hz)	Pulses	Anode	Cathode	Current (mA)	Electrode Size (cm^2)	Duration	Localization Method	Sham
Fregni, 2008 [57]	R a-tDCS L a-tDCS	–	–	–	–	R L	L R	2	35	20	EEG	Turned off after 30 s
Gluck, 2015 [62•]	a-tDCS c-tDCS	–	–	–	–	L L	R Supraorbital L Forearm	2	25	40	EEG	30 s and ramped down over 1 min
Goldman, 2011 [56]	a-tDCS	–	–	–	–	R	L	2	Not Stated	20	EEG	Turned off after 15 s
Jauch-Chara, 2014 [61]	a-tDCS	–	–	–	–	R	L Supraorbital	–	35	20	5 cm anterior M1[b]	identical set up no current
Kekic, 2014 [55]	a-tDCS	–	–	–	–	R	L	2	25	20	EEG	Turned off after 30 s
Lapenta, 2014 [6]	a-tDCS	–	–	–	–	R	L	–	35	20	EEG	Turned off after 15 s
Montenegro, 2012 [59]	a-tDCS	–	–	–	–	L	R Supraorbital	1	35	20	EEG	Turned off after 30 s
Barth, 2011 [41]	rTMS	L	100	10	3000	–	–	–	–	15	5 cm anterior M1	Electrodes and sham coil
Lowe, 2014 [49]	cTBS	L	80	50[a]	600	–	–	–	–	40s	EEG	Rotated coil
Uher, 2005 [40]	rTMS	L	110	–	1000	–	–	–	–	20	EEG	Sham coil
Van den Eynde, 2010 [42]	rTMS	L	110	–	1000	–	–	–	–	–	EEG	Sham coil
Kekic, unpublished data [64]	R a-tDCS L a-tDCS	–	–	–	–	R L	L R	–	–	20	EEG	Turned off after 30 s

a-tDCS, anodal tDCS; *c-tDCS*, cathodal tDCS; *NBIS*, non-invasive brain stimulation

[a] Stimulation was applied in the theta burst pattern (3 pulses at 50 Hz every 200 ms)

[b] M1 = primary motor cortex

Unless otherwise specified, R refers to the right dlPFC and L refers to the left dlPFC. EEG refers to the use of the international 10–20 system to localize the dlPFCC

(From: Lowe CJ, et al. Psychosomatic Medicine;79:2–13, with permission from Wolters Kluwer Health, Inc.) [64]

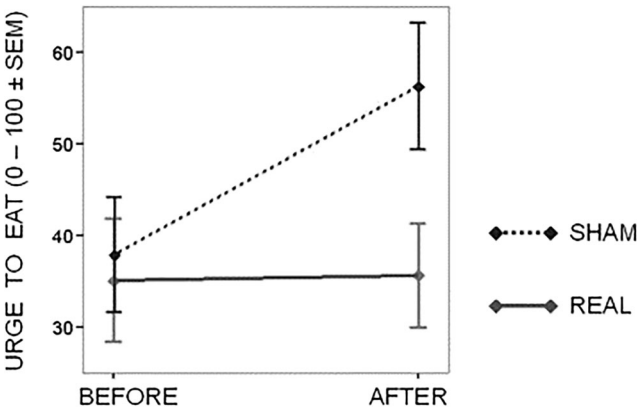

Fig. 1 Self-reported craving before and after real or sham repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. (From: Uher R, et al. *Biological Psychiatry* 2005;58(10):840–2.DOI: https://doi.org/10.1016/j.biopsych.2005.05.043, with permission from Elsevier) [40]

the superficial cortical region. The current then proceeds out of the cathode where neural activity is inhibited through hyperpolarization of neurons [51]. Unlike with rTMS, risks and side effects from tDCS are minimal [52, 53] and it has therefore been more widely utilized in studies of appetitive behaviors compared with other neuromodulation techniques.

In particular, several recent studies have demonstrated reduced food craving [6, 54••, 55–59], ratings of hunger, and desire to eat [59] and food intake [6, 55–57, 60•, 61, 62•] after 1 or more tDCS sessions aimed at enhancing both right [6, 54••, 55–58, 61] and left [57, 59, 60•, 62•] dlPFC activity in lean [6, 54••, 55, 57, 61] and overweight [54••, 56, 59]/obese [60•, 62•] individuals, as well as individuals with BED [58]. A proof of principle study from our lab demonstrated participants with obesity receiving anodal versus cathodal tDCS to the left DLPFC tended to have lower ad libitum energy intake during an inpatient vending machine paradigm, and significant decrease in weight [62•]. In a follow-up study, those receiving active tDCS had decreased hunger ratings (Fig. 2) and reduced ad libitum snack food intake following 5 weeks of active tDCS to the left dlPFC [60•] (Fig. 3). Overall, findings support tDCS as a useful tool for potentially modifying activity of the prefrontal cortex and decreasing craving, food intake, and weight.

NIBS: Remaining Controversies and Future Directions

The increasing number of studies utilizing NIBS techniques to study eating behavior has opened exciting new horizons. However, there are numerous issues that lack consensus in the field and much work that remains to be accomplished. Although an in-depth discussion of these issues is outside the scope of this paper, see Hall et al. 2018 [39••] for a comprehensive review of current controversies and future directions concerning the use of NIBS on cravings, food consumption, and eating disorders. One primary inconsistency in the field concerns target regions and dose/duration of treatment. Compared with rTMS, a greater number of multi-session studies have been conducted using tDCS to examine the longer-term effects of neuromodulation on food craving and consumption [26••]. However, the majority of previous studies have utilized single-session treatments [6, 40–42, 45, 46, 55–59] whereas fewer have examined the efficacy of rTMS [43, 44, 47, 48••] or tDCS [54••, 58, 60•, 61, 62•] over the longer term. Additionally, all but two [60•, 62•] studies were ambulatory; thus, effects beyond immediate changes in food craving or food intake in the laboratory require future study. Because of the lack of longitudinal data, we are unable to assess the efficacy of NIBS over the longer term.

Additionally, some controversy also remains over the most effective target region [39••]. In the seminal paper of neuroimaging and obesity [8••], lesser activation in the left DLPFC was observed following a meal in obese vs. lean individuals implicating this region as an appropriate target for intervention. However, in the studies outlined here, NIBS was conducted following a specified length of time after the last meal (ranging from a minimum of 2 h [42] to an overnight fast [60•, 62•]). Future studies should assess the efficacy of NIBS immediately following a meal and/or compare pre vs. post meal effects. Regarding laterality, one recent meta-analysis concluded that there was not an overall difference in the effects of left vs. right anodal dlPFC stimulation on different forms of craving [63]. Although it has been suggested that the target region (left vs. right) is often confounded with methodology in that most rTMS studies target the left compared with tDCS studies which primarily have targeted the right DLPFC [64].

An area of focus that is recently garnering interest involves the large inter-individual [39••, 64] and response variability observed within studies [65•]. It has been widely agreed upon that mechanistic studies are needed [50] to help address methodological issues. One recent study examined the contribution of catechol-O-methyl transferase (COMT) Val158Met genotypic variability to tDCS effects on appetite [65•]. They observed that COMT Met allele carriers receiving active tDCS responded better to tDCS, demonstrating lower levels of hunger, desire to eat, and prospective consumption over time compared with Met non-carriers, who did not respond [65•]. Results from this study underscore the importance of taking inter-individual variability into account when designing and interpreting future studies involving NIBS interventions.

Summary and Conclusion

Brain stimulation techniques offer promising results in modulating food intake and eating behaviors and have been pivotal for helping to elucidate the underlying neural and cognitive mechanisms regulating appetitive behaviors.

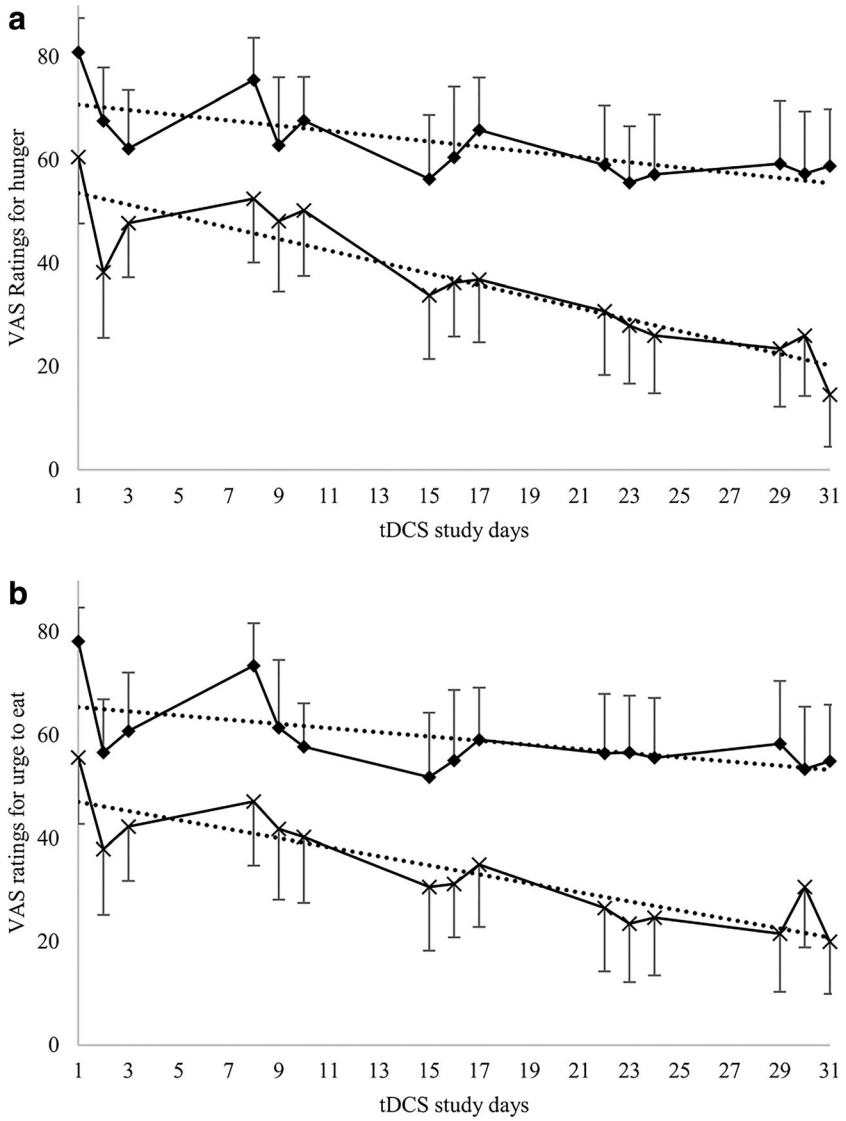

Fig. 2 Effect of anodal compared with sham tDCS on VAS ratings during tDCS sessions. VAS ratings of hunger (**a**) and the urge to eat (**b**) during the inpatient assessment (tDCS study days 1–3) and outpatient visits (tDCS study days 8–31), comparing anodal (×) and sham (◆) stimulation, relative to study days after the first stimulation session. Means of ratings before and after tDCS are shown for all individuals within 1 study group. A total of 29 individuals complete the inpatient assessment (anodal tDCS, $n = 13$; sham tDCS, $n = 16$), and 23 completed the outpatient assessment (anodal tDCS, $n = 9$; sham tDCS, $n = 14$). Relative to the sham group, individuals receiving anodal tDCS had a greater decrease in VAS ratings for hunger and the urge to eat ($P = 0.01$; β, −0.61 VAS score/d; SE, 0.22 VAS score/d; df, 610; t value, 2.69; and $P = 0.05$; β, −0.46 VAS score/d; SE, 0.23 VAS score/d; df, 610; t value, 1.96, respectively) in a mixed model adjusted for age and sex, as indicated by the significant difference in the slope for these ratings comparing both groups over time ($P = 0.01$ and $P = 0.05$, respectively). *Dotted lines* represent trendlines for the decrease in ratings. For hunger ratings **(a)**, the slopes of the trendlines for sham compared with anodal tDCS are −0.51 ($P = 0.003$) and −1.11 ($P < 0.0001$), respectively. VAS ratings for the urge to eat **(b)** display a steeper decrease in the anodal group (slope = −0.87; $P < 0.0001$) compared with the sham group (slope = −0.41; $P = 0.02$). Absolute VAS ratings of hunger and the urge to eat were consistently lower in the anodal group, including those ratings given before the first tDCS session. Because no identifiable baseline differences were found in the anodal and sham groups (all $P > 0.05$), consistently lower VAS ratings of hunger and the urge to eat in the anodal compared with the sham group is likely because of the relatively small study cohort. Of note, however, assessment of the greater declines in hunger and the urge to eat in mixed models accounted for the baseline ratings. tDCS, transcranial direct current stimulation; VAS, visual analog scale. (From: Heinitz S, et al. The American Journal of Clinical Nutrition, Volume 106, Issue 6, December 2017, Pages 1347–1357, https://doi.org/10.3945/ajcn.117.158089, by permission of Oxford University Press) [60•]

rTMS and tDCS are promising technologies for treating diseases characterized by dysregulated eating behavior such as obesity, AN, BN, and BED, as they are noninvasive and easy to administer and have few side effects or complications relative to invasive techniques such as DBS or VNS. In certain severe cases of AN or very

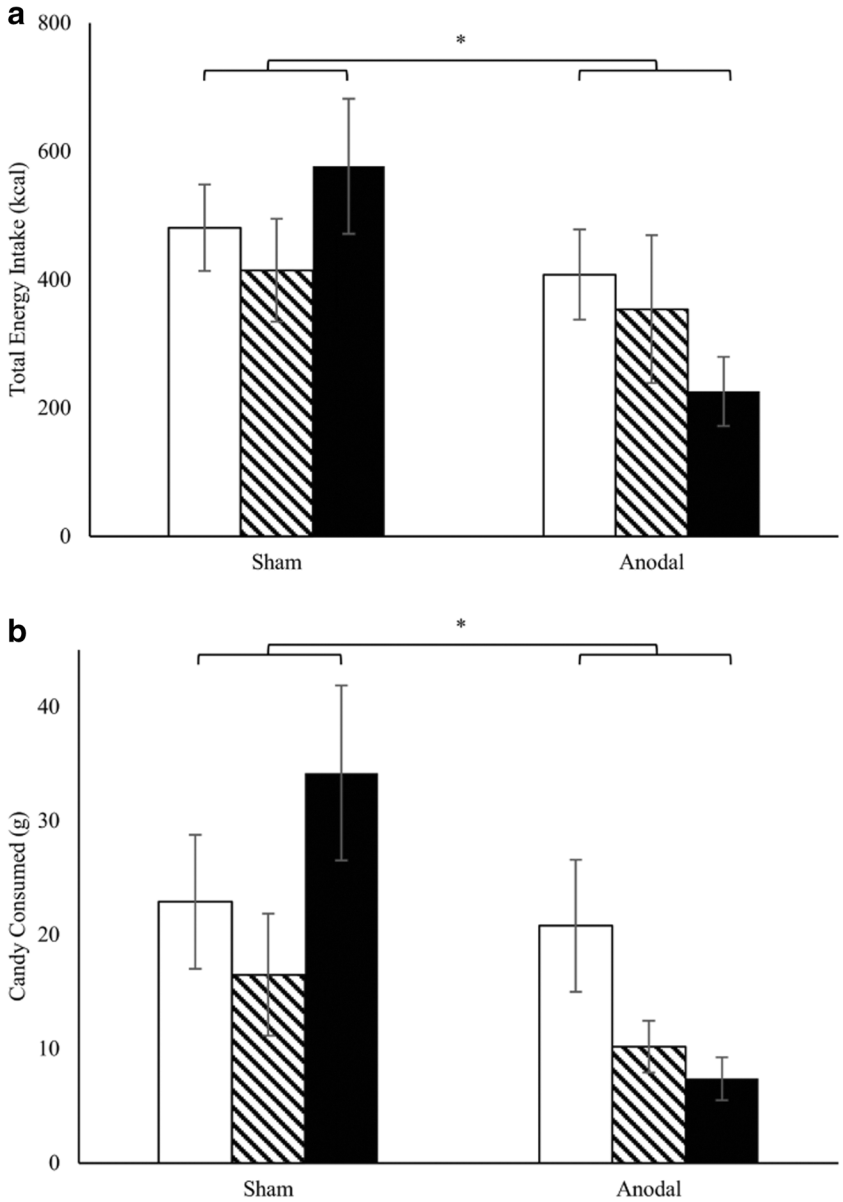

Fig. 3 Effect of anodal compared with sham tDCS on food intake during SFTT. Total energy intake (kilocalories; **a**) and candy consumed (grams; **b**) during SFTT 1 (first test during the baseline assessment; *white columns*), SFTT 2 (last test during the baseline assessment; *striped columns*), and SFTT 3 (test on the last day of the study during the outpatient visits; *black columns*). For baseline assessment (11 d), anodal and sham tDCS was performed in 13 and 16 subjects, respectively. Snack food intake could be analyzed in 8 and 13 individuals in the anodal and sham tDCS groups, respectively, during the outpatient assessment (4 consecutive weeks). SFTT1 and SFTT3 were compared, and relative to those who received sham tDCS, individuals who received anodal stimulation had significantly lower total energy intake (df, 1; *t* value, 2.77) and ate less candy (df, 1; *t* value, 2.95), as assessed with ANCOVA; this indicates an effect of anodal (compared with sham) tDCS on energy intake and thus indirectly on eating behavior in this setting. In a mixed model, time-by-treatment interaction for total energy intake and for candy consumed is $P = 0.05$. SFTT, snack food taste test; tDCS, transcranial direct current stimulation. *$P < 0.05$. (From: Heinitz S, et al. The American Journal of Clinical Nutrition, Volume 106, Issue 6, December 2017, Pages 1347–1357, https://doi.org/10.3945/ajcn.117.158089, by permission of Oxford University Press) [60•]

severe obesity, the potentially therapeutic benefits of DBS may outweigh the risks of side effects.

While there is evidence that modulating neuronal excitability in executive, reward, and homeostatic regions of the brain may temporarily influence food craving and food intake behavior, there is a need for follow-up research to assess whether such treatments are beneficial as long-term strategies for improving health outcomes. Studies combining neuroimaging and NIBS are scarce yet could be crucial for providing a greater understanding of the neuromodulatory mechanisms of action and improve identification of treatment targets. Future research should continue to focus on identifying optimal frequency and duration of stimulation and employ multi-session longitudinal

studies of NIBS to assess potential side effects and the long-term effectiveness on clinical outcomes such as weight loss and sustained improvements in eating behaviors over time.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animals Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, instructional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Michaud A, Vainik U, Garcia-Garcia I, Dagher A. Overlapping neural endophenotypes in addiction and obesity. Front Endocrinol. 2017;8:127. https://doi.org/10.3389/fendo.2017.00127.
2. Volkow ND, Wise RA. How can drug addiction help us understand obesity? Nat Neurosci. 2005;8(5):555–60.
3. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. Obes Rev. 2013;14(1):2–18.
4. Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE. The contribution of brain reward circuits to the obesity epidemic. Neurosci Biobehav Rev. 2013;37(9):2047–58.
5. Monteleone AM, Castellini G, Volpe U, Ricca V, Lelli L, Monteleone P, et al. Neuroendocrinology and brain imaging of reward in eating disorders: a possible key to the treatment of anorexia nervosa and bulimia nervosa. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;80:132–42.
6. Lapenta OM, Di Sierve K, de Macedo EC, Fregni F, Boggio PS. Transcranial direct current stimulation modulates ERP-indexed inhibitory control and reduces food consumption. Appetite. 2014;83:42–8.
7. Gluck ME, Viswanath P, Stinson EJ. Obesity, appetite, and the prefrontal cortex. Curr Obes Rep. 2017;6(4):380–8. https://doi.org/10.1007/s13679-017-0289-0.
8. •• Le DS, Pannacciulli N, Chen K, Del Parigi A, Salbe AD, Reiman EM, et al. Less activation of the left dorsolateral prefrontal cortex in response to a meal: a feature of obesity. Am J Clin Nutr. 2006;84(4):725–31. https://doi.org/10.1093/ajcn/84.4.725. **Seminal study demonstrating lesser dlPFC activation in obese vs. lean.**
9. Le DS, Pannacciulli N, Chen K, Salbe AD, Del Parigi A, Hill JO, et al. Less activation in the left dorsolateral prefrontal cortex in the reanalysis of the response to a meal in obese than in lean women and its association with successful weight loss. Am J Clin Nutr. 2007;86(3):573–9. https://doi.org/10.1093/ajcn/86.3.573.
10. Le DS, Chen K, Pannacciulli N, Gluck M, Reiman EM, Krakoff J. Reanalysis of the obesity-related attenuation in the left dorsolateral prefrontal cortex response to a satiating meal using gyral regions-of-interest. J Am Coll Nutr. 2009;28(6):667–73.
11. •• Lowe CJ, Reichelt AC, Hall PA. The prefrontal cortex and obesity: a health neuroscience perspective. Trends Cogn Sci. 2019 Apr;23(4):349–61. https://doi.org/10.1016/j.tics.2019.01.005. **Comprehensive review highlighting the relationship between obesity and the prefrontal cortex.**
12. Kumar R, Simpson CV, Froelich CA, Baughman BC, Gienapp AJ, Sillay KA. Obesity and deep brain stimulation: an overview. Ann Neurosci. 2015;22(3):181–8.
13. Lee DJ, Elias GJB, Lozano AM. Neuromodulation for the treatment of eating disorders and obesity. Therapeut Adv Psychopharmacol. 2018;8(2):73–92. https://doi.org/10.1177/2045125317743435.
14. Herrington T, Eskandar E. 24 - deep brain stimulation. In: Kumar MKW, Levine JM, Schuster J, editors. Neurocritical care management of the neurosurgical patient. London: Elsevier; 2018. p. 241–51.
15. Formolo DA, Gaspar JM, Melo HM, Eichwald T, Zepeda RJ, Latini A, et al. Deep brain stimulation for obesity: a review and future directions. Front Neurosci. 2019;13:323. https://doi.org/10.3389/fnins.2019.00323.
16. Ruffin M, Nicolaidis S. Electrical stimulation of the ventromedial hypothalamus enhances both fat utilization and metabolic rate that precede and parallel the inhibition of feeding behavior. Brain Res. 1999;846(1):23–9. https://doi.org/10.1016/s0006-8993(99)01922-8.
17. Bielajew C, Stenger J, Schindler D. Factors that contribute to the reduced weight gain following chronic ventromedial hypothalamic stimulation. Behav Brain Res. 1994;62(2):143–8.
18. Whiting DM, Tomycz ND, Bailes J, de Jonge L, Lecoultre V, Wilent B, et al. Lateral hypothalamic area deep brain stimulation for refractory obesity: a pilot study with preliminary data on safety, body weight, and energy metabolism. J Neurosurg. 2013;119(1):56–63. https://doi.org/10.3171/2013.2.jns12903.
19. Tronnier VM, Rasche D, Thorns V, Alvarez-Fischer D, Munte TF, Zurowski B. Massive weight loss following deep brain stimulation of the nucleus accumbens in a depressed woman. Neurocase. 2018;24(1):49–53. https://doi.org/10.1080/13554794.2018.1431678.
20. Wu H, Van Dyck-Lippens PJ, Santegoeds R, van Kuyck K, Gabriëls L, Lin G, et al. Deep-brain stimulation for anorexia nervosa. World Neurosurg. 2013;80(3–4):S29 e1-S. e10.
21. Lipsman N, Lam E, Volpini M, Sutandar K, Twose R, Giacobbe P, et al. Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial. Lancet Psychiatry. 2017;4(4):285–94. https://doi.org/10.1016/s2215-0366(17)30076-7.
22. Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM. The subcallosal cingulate gyrus in the context of major depression. Biol Psychiatry. 2011;69(4):301–8. https://doi.org/10.1016/j.biopsych.2010.09.034.
23. Browning KN, Verheijden S, Boeckxstaens GE. The Vagus nerve in appetite regulation, mood, and intestinal inflammation. Gastroenterology. 2017;152(4):730–44. https://doi.org/10.1053/j.gastro.2016.10.046.
24. Pelot NA, Grill WM. Effects of vagal neuromodulation on feeding behavior. Brain Res. 2018;1693(Pt B:180–7. https://doi.org/10.1016/j.brainres.2018.02.003.
25. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res. 2018;11:203–13. https://doi.org/10.2147/jir.s163248.
26. •• Val-Laillet D, Aarts E, Weber B, Ferrari M, Quaresima V, Stoeckel LE, et al. Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. NeuroImage Clin. 2015;8:1–31. https://doi.org/10.1016/j.nicl.2015.03.016. **Comprehensive review of neuromodulation and**

neuroimaging techniques in the study of obesity and eating disorders.

27. Bodenlos JS, Schneider KL, Oleski J, Gordon K, Rothschild AJ, Pagoto SL. Vagus nerve stimulation and food intake: effect of body mass index. J Diabetes Sci Technol. 2014;8(3):590–5. https://doi.org/10.1177/1932296814525188.
28. Manning KE, McAllister CJ, Ring HA, Finer N, Kelly CL, Sylvester KP, et al. Novel insights into maladaptive behaviours in Prader-Willi syndrome: serendipitous findings from an open trial of vagus nerve stimulation. J Intellect Disability Res : JIDR. 2016;60(2):149–55. https://doi.org/10.1111/jir.12203.
29. Ikramuddin S, Blackstone RP, Brancatisano A, Toouli J, Shah SN, Wolfe BM, et al. Effect of reversible intermittent intra-abdominal vagal nerve blockade on morbid obesity: the ReCharge randomized clinical trial. Jama. 2014;312(9):915–22. https://doi.org/10.1001/jama.2014.10540.
30. Sarr MG, Billington CJ, Brancatisano R, Brancatisano A, Toouli J, Kow L, et al. The EMPOWER study: randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity. Obes Surg. 2012;22(11):1771–82. https://doi.org/10.1007/s11695-012-0751-8.
31. Song S, Zilverstand A, Gui W, Li HJ, Zhou X. Effects of single-session versus multi-session non-invasive brain stimulation on craving and consumption in individuals with drug addiction, eating disorders or obesity: a meta-analysis. Brain Stimul. 2019;12(3):606–18. https://doi.org/10.1016/j.brs.2018.12.975.
32. Rachid F. Repetitive transcranial magnetic stimulation in the treatment of eating disorders: a review of safety and efficacy. Psychiatry Res. 2018;269:145–56. https://doi.org/10.1016/j.psychres.2018.08.013.
33. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol : Off J Int Fed Clin Neurophysiol. 2009;120(12):2008–39. https://doi.org/10.1016/j.clinph.2009.08.016.
34. Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. Int J Neuropsychopharmacol. 2008;11(1):131–47. https://doi.org/10.1017/s1461145707007717.
35. Johann M, Wiegand R, Kharraz A, Bobbe G, Sommer G, Hajak G, et al. Repetitiv transcranial magnetic stimulation in nicotine dependence. Psychiatr Prax. 2003;30(Suppl 2):129–31.
36. Camprodon JA, Martinez-Raga J, Alonso-Alonso M, Shih MC, Pascual-Leone A. One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. Drug Alcohol Depend. 2007;86(1):91–4. https://doi.org/10.1016/j.drugalcdep.2006.06.002.
37. Eichhammer P, Johann M, Kharraz A, Binder H, Pittrow D, Wodarz N, et al. High-frequency repetitive transcranial magnetic stimulation decreases cigarette smoking. J Clin Psychiatry. 2003;64(8):951–3.
38. Lapenta OM, Marques LM, Rego GG, Comfort WE, Boggio PS. tDCS in addiction and impulse control disorders. J ECT. 2018;34(3):182–92. https://doi.org/10.1097/yct.0000000000000541.
39.•• Hall PA, Vincent CM, Burhan AM. Non-invasive brain stimulation for food cravings, consumption, and disorders of eating: a review of methods, findings and controversies. Appetite. 2018;124:78–88. https://doi.org/10.1016/j.appet.2017.03.006. **Recent and updated review of rTMS and tDCS that provides a comprehensive discussion of current debates and future directions**.
40. Uher R, Yoganathan D, Mogg A, Eranti SV, Treasure J, Campbell IC, et al. Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. Biol Psychiatry. 2005;58(10):840–2.
41. Barth KS, Rydin-Gray S, Kose S, Borckardt JJ, O'Neil PM, Shaw D, et al. Food cravings and the effects of left prefrontal repetitive transcranial magnetic stimulation using an improved sham condition. Front Psychiatr. 2011;2:9. https://doi.org/10.3389/fpsyt.2011.00009.
42. Van den Eynde F, Claudino AM, Mogg A, Horrell L, Stahl D, Ribeiro W, et al. Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. Biol Psychiatry. 2010;67(8):793–5.
43. Downar J, Sankar A, Giacobbe P, Woodside B, Colton P. Unanticipated rapid remission of refractory bulimia nervosa, during high-dose repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex: a case report. Front Psychiatr. 2012;3:30.
44. Gay A, Jaussent I, Sigaud T, Billard S, Attal J, Seneque M, et al. A lack of clinical effect of high-frequency r TMS to dorsolateral prefrontal cortex on bulimic symptoms: a randomised, double-blind trial. Eur Eat Disord Rev. 2016;24(6):474–81.
45. Sutoh C, Koga Y, Kimura H, Kanahara N, Numata N, Hirano Y, et al. Repetitive transcranial magnetic stimulation changes cerebral oxygenation on the left dorsolateral prefrontal cortex in bulimia nervosa: a near-infrared spectroscopy pilot study. Eur Eat Disord Rev : J Eat Disord Assoc. 2016;24(1):83–8. https://doi.org/10.1002/erv.2413.
46. Van den Eynde F, Guillaume S, Broadbent H, Campbell IC, Schmidt U. Repetitive transcranial magnetic stimulation in anorexia nervosa: a pilot study. Eur Psychiatr : J Assoc Eur Psychiatrists. 2013;28(2):98–101. https://doi.org/10.1016/j.eurpsy.2011.06.002.
47. McClelland J, Kekic M, Campbell IC, Schmidt U. Repetitive transcranial magnetic stimulation (rTMS) treatment in enduring anorexia nervosa: a case series. Eur Eating Disord Rev : J Eat Disord Assoc. 2016;24(2):157–63. https://doi.org/10.1002/erv.2414.
48.•• Dalton B, Bartholdy S, McClelland J, Kekic M, Rennalls SJ, Werthmann J, et al. Randomised controlled feasibility trial of real versus sham repetitive transcranial magnetic stimulation treatment in adults with severe and enduring anorexia nervosa: the TIARA study. BMJ Open. 2018;8(7):e021531. https://doi.org/10.1136/bmjopen-2018-021531. **Preliminary evidence for feasibility, patient acceptability, and efficacy of rTMS treatment for SE-AN**.
49. Lowe CJ, Hall PA, Staines WR. The effects of continuous theta burst stimulation to the left dorsolateral prefrontal cortex on executive function, food cravings, and snack food consumption. Psychosom Med. 2014;76(7):503–11.
50. Bikson M, Paulus W, Esmaeilpour Z, Kronberg G, Nitsche MA. Mechanisms of acute and after effects of transcranial direct current stimulation. In: Knotkova H, Nitsche MA, Bikson M, Woods AJ, editors. Practical guide to transcranial direct current stimulation: principles, procedures and applications. Cham: Springer International Publishing; 2019. p. 81–113.
51. Lang N, Nitsche MA, Paulus W, Rothwell JC, Lemon RN. Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. Exp Brain Res. 2004;156(4):439–43. https://doi.org/10.1007/s00221-003-1800-2.
52. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol : Off J Int Fed Clin Neurophysiol. 2006;117(4):845–50. https://doi.org/10.1016/j.clinph.2005.12.003.
53. Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology. 2005;64(5):872–5. https://doi.org/10.1212/01.wnl.0000152986.07469.e9.
54.•• Ljubisavljevic M, Maxood K, Bjekic J, Oommen J, Nagelkerke N. Long-term effects of repeated prefrontal cortex transcranial direct

current stimulation (tDCS) on food craving in normal and overweight young adults. Brain Stimul. 2016;9(6):826–33. https://doi.org/10.1016/j.brs.2016.07.002. **Longitudinal study that showed the beneficial long-term effects of repeated tDCS to the dlPFC resulted in decreased food craving after a single session and had a significant effect which remained after 30 days**.

55. Kekic M, McClelland J, Campbell I, Nestler S, Rubia K, David AS, et al. The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. Appetite. 2014;78:55–62.
56. Goldman RL, Borckardt JJ, Frohman HA, O'Neil PM, Madan A, Campbell LK, et al. Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. Appetite. 2011;56(3):741–6. https://doi.org/10.1016/j.appet.2011.02.013.
57. Fregni F, Orsati F, Pedrosa W, Fecteau S, Tome FA, Nitsche MA, et al. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite. 2008;51(1):34–41. https://doi.org/10.1016/j.appet.2007.09.016.
58. Burgess EE, Sylvester MD, Morse KE, Amthor FR, Mrug S, Lokken KL, et al. Effects of transcranial direct current stimulation (tDCS) on binge eating disorder. Int J Eat Disord. 2016;49(10):930–6. https://doi.org/10.1002/eat.22554.
59. Montenegro RA, Okano AH, Cunha FA, Gurgel JL, Fontes EB, Farinatti PT. Prefrontal cortex transcranial direct current stimulation associated with aerobic exercise change aspects of appetite sensation in overweight adults. Appetite. 2012;58(1):333–8. https://doi.org/10.1016/j.appet.2011.11.008.
60.• Heinitz S, Reinhardt M, Piaggi P, Weise CM, Diaz E, Stinson EJ, et al. Neuromodulation directed at the prefrontal cortex of subjects with obesity reduces snack food intake and hunger in a randomized trial. Am J Clin Nutrit. 2017;106(6):1347–57. https://doi.org/10.3945/ajcn.117.158089. **Demonstrated reduced hunger ratings and ad libitum snack food consumption in satiated individuals after a longer- but not shorter-term anodal tDCS to the ldLPFC**.
61. Jauch-Chara K, Kistenmacher A, Herzog N, Schwarz M, Schweiger U, Oltmanns KM. Repetitive electric brain stimulation reduces food intake in humans. Am J Clin Nutr. 2014;100(4):1003–9.
62.• Gluck ME, Alonso-Alonso M, Piaggi P, Weise CM, Jumpertz-von Schwartzenberg R, Reinhardt M, et al. Neuromodulation targeted to the prefrontal cortex induces changes in energy intake and weight loss in obesity. Obesity. 2015;23(11):2149–56. **First study to show association of tDCS to the left dlPFC with decreased food intake and weight loss in adults with obesity**.
63. Jansen JM, Daams JG, Koeter MW, Veltman DJ, van den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci Biobehav Rev. 2013;37(10 Pt 2):2472–80. https://doi.org/10.1016/j.neubiorev.2013.07.009.
64. Lowe CJ, Vincent C, Hall PA. Effects of noninvasive brain stimulation on food cravings and consumption: a meta-analytic review. Psychosom Med. 2017;79(1):2–13. https://doi.org/10.1097/psy.0000000000000368.
65.• Fassini PG, Das SK, Suen VMM, Magerowski G, Marchini JS, da Silva Junior WA, et al. Appetite effects of prefrontal stimulation depend on COMT Val158Met polymorphism: a randomized clinical trial. Appetite. 2019;140:142–50. https://doi.org/10.1016/j.appet.2019.05.015. **First study to show that genotype differences impacting dopamine levels influenced prefrontal tDCS effects on appetite, concluding that inter-individual sources of variability should be considered in future studies**.