Effective transcranial direct current stimulation (tDCS) parameters for the modulation of eating behavior: A systematic literature review and meta-analysis

Running title: Effective tDCS parameters for eating behavior

Jordan D. Beaumont MMedSci[a,*], Natalie C. Smith[a], David Starr BSc[a], Danielle Davis PhD[a], Michelle Dalton PhD[a], Alexander Nowicky PhD[b], Mark Russell PhD[a] and Martin J. Barwood PhD[a]

[a]*School of Social and Health Sciences, Leeds Trinity University, Leeds, LS18 5HD, UK*

[b]*Centre for Cognitive Neuroscience, Department of Clinical Sciences, College of Health and Life Sciences, Brunel University London, Uxbridge, UB8 3PH, UK*

*** Corresponding author:**

Jordan D. Beaumont

School of Social and Health Sciences, Leeds Trinity University, Leeds, LS18 5HD, UK

Email: j.beaumont@leedstrinity.ac.uk

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ABSTRACT

Objective

To consider the effect of differing transcranial direct current stimulation (tDCS) parameters on eating-related measures, and how issues with experimental design (e.g., inadequate blinding) or parameters variation may drive equivocal effects.

Methods

Literature searches were conducted across MEDLINE, PsycINFO, Scopus, and Science Direct. Studies using conventional sham-controlled tDCS to modify eating-related measures in adult human participants were included. A total of 1,135 articles were identified and screened by two independent authors. Study quality was assessed using the Risk of Bias tool. Random-effect meta-analyses were performed, with subgroup analyses to determine differences between parameter sets.

Results

We identified 28 eligible studies; seven showed low risk of bias, with the remaining studies showing bias arising from issues implementing or reporting blinding protocols. Large variation in applied parameters was found, including montage, current intensity and density, participant and researcher blinding, and the use of online or offline tasks. The application of differing parameters appeared to alter the effects of tDCS on eating-related measures, particularly for current density (g = -0.25 to 0.31), and when comparing single-session (g = -0.08 to 0.01) versus multi-session protocols (g = -0.34 to -0.29). Some parameters result in null effects.

Conclusion

The absence of tDCS-mediated change in eating-related measures may be driven by variation in applied parameters. Consistent application of parameters which appear effective for modulating eating behavior is important for identifying the potential impact of tDCS. Using

the findings of this review, we propose a series of parameters that researchers should apply in their work.

KEYWORDS

Appetite, Food consumption, Food craving, Food reward, Neuromodulation, Non-invasive brain stimulation

ACRONYMS

CI = confidence interval; cm = centimeter; COMT = catechol-o-methyl transferase; DLPFC = dorsolateral prefrontal cortex; EBA = extrastriate body area; *g* = Hedges' *g*; IFG = inferior frontal gyrus; mA = milliampere; NIBS = non-invasive brain stimulation; PFC = prefrontal cortex; PICO = Population, Intervention, Control and Outcome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RoB = risk of bias; SD = standard deviation; SE = standard error; tDCS = transcranial direct current stimulation; tnM1 = tongue muscle representation of the primary motor cortex

1. INTRODUCTION

Over the last decade there has been increasing interest in the use of non-invasive brain stimulation (NIBS) techniques, particularly transcranial direct current stimulation (tDCS), for modifying eating behaviors associated with overconsumption and weight gain. Through tDCS, a constant weak electrical current is applied to the brain via electrodes connected to a battery-powered device (1, 2). Although the current strength is not sufficient to cause neuronal firing, it appears able to modulate resting membrane potentials in a polarity-dependent manner through inhibition of neurotransmitters such as gamma-aminobutyric acid and glutamate (3, 4). The electric current is delivered through an anode (positive charge) electrode, where it is passed through the brain to a cathode (negative charge) electrode and is returned to the device. In a simplistic view, the anode is associated with depolarization of cortical activity and an increased likelihood of spontaneous neuronal firing. Conversely, the cathode is associated with hyperpolarization of the cortex resulting in the decreased likelihood of spontaneous neuronal firing (3).

The ability of tDCS to alter eating behaviors, such as food craving and consumption, has been of great interest for researchers due to its potential use in the treatment of obesity (5). Since the first study using tDCS to alter food craving was published over a decade ago (6), the potential for this technique to improve hedonic appetite control has seen an increase in published data. However, despite the promising effects outlined in this early study, more recent data shows equivocal effects (7-10). This may be due to a lack of replication of data as studies have employed varying designs (e.g., between- and within-group design), outcome measures and stimulation parameters. The modulatory effects of tDCS are driven largely by the specific stimulation parameters and device set-up (11). This includes the electrode montage, current intensity and density, stimulation duration, and number of sessions. Online protocols may also impact the modulatory effects (12). Despite the evident variation caused by altering stimulation parameters, these parameters can vary greatly between studies resulting in large variation in data (4, 13). This demonstrates the importance

of identifying and consistently applying parameters that are known to modulate the outcome measure. This is not a new concept (3, 12, 14), but has not been discussed in-depth for studies measuring eating-related outcomes.

Understanding the ability of tDCS to modify eating behaviors is particularly difficult with variation in study design, outcome measures and stimulation parameters. If indeed this technique is to be used as an additional or adjunctive treatment modality for weight management, it is important that these inconsistencies are addressed (15). Here we expand on recent reviews (16, 17) to provide further detail on the potential impact of different stimulation parameters and widen the discussion to incorporate important parameter considerations, including reference electrode placement, electrode size, current density, blinding efficacy, and the use of offline/online protocols. Specifically, we aim to identify effective tDCS parameter ranges for the modulation of eating behavior, and determine whether null effects are driven by parameters outside of these ranges.

2. METHODS

2.1. Search Strategy

An electronic literature search was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18) (Table S1). The literature search was completed using MEDLINE, PsycINFO and Scopus databases in March 2019, and repeated in July 2020 to include additional articles published during this time. Search terms are displayed in Table 1. An additional search was conducted using the Science Direct database. Due to restrictions on Boolean terms and wildcards (*), revised search terms were used (Table 1). Results were limited to those written in English and published after 1998 to coincide with the development of modern tDCS procedures (2, 19).

***** INSERT TABLE 1 HERE *****

2.2. Inclusion and Exclusion Criteria

After removing duplicates (n = 248), titles and abstracts were assessed for inclusion. Where elimination based on title and abstract was not possible, full-text articles were retrieved and assessed for inclusion in the final sample. Reviews, abstracts (where full-text articles were unavailable), editorials/commentaries, book chapters, theses, study protocols, case reports and animal studies were not included in the present review (total n = 68). Articles were assessed in line with the Population, Intervention, Criteria and Outcome (PICO) model (20). Articles were included if they were peer-reviewed intervention studies that recruited adult human participants *(population)*, applying conventional tDCS (i.e., one anode, one cathode) procedures *(intervention)* which were sham-controlled *(control)*, and reported an outcome measure relating to eating behavior (food craving, food consumption, food reward, subjective appetite) *(outcome)*. Article selection was performed by two independent authors (JDB and DS). Any further articles known to the authors were also considered for inclusion.

2.3. Data Extraction

For each eligible study, the following data were extracted: names of authors; year of publication; participant characteristics; montage and electrode size; current intensity and density; stimulation duration; ramp duration; sham protocol; number of sessions; blinding efficacy; use of online and offline protocols; outcome measures; main findings. Data were extracted as reported in the original article(s) by JDB.

2.4. Study Quality Assessment

The quality of studies was determined using the Cochrane Collaboration's Risk of Bias (RoB) tool (21). Judgements were made by two independent authors at the study level; agreement between authors (JDB and NCS) was high ($\kappa = 0.93$). This data will be used to identify issues with study design, particularly in relation to the delivery of tDCS.

2.5. Meta-Analysis

Means, standard deviations (SD) and sample size were extracted for eating-related measures. Where standard error (SE) was reported, SD was estimated using the equation $SD = SE \times \sqrt{n}$ (20). If data were not reported, datasets were requested from corresponding authors. Otherwise, means and SD or SE were extracted from available figures using WebPlotDigitizer (version 4.4) (22), or estimated using the Practical Meta-Analysis Effect Size Calculator (23) by entering *t* or *F* statistic and sample size. If data or effect sizes were estimated, these were validated by two authors independently (JDB and NCS). Standardized mean differences were calculated and adjusted using Hedges' *g* due to small sample size (n < 20) across many of the reviewed articles.

Analyses focused on single-session tDCS, to remove the potential cumulative effect of multi-session protocols. Four studies did not measure the effects of single-session tDCS and were removed from analyses (24-27). Additional studies were removed due to missing data (28) or due to all participants receiving active tDCS (29). To reduce confounding analyses, the expectation effect observed by Ray et al. (30) was also removed. A total of 21 studies (n = 743 participants) were included in the meta-analysis (Table S5). Where possible, separate analyses comparing single- versus multi-session tDCS were completed to identify any cumulative effect (additional n = 3 studies, 105 participants). Where effect sizes are based on composite scores (i.e., mean scores across varying levels of a specific parameter) within the same participant group, these were removed from analyses for the specific parameter measure to avoid confounding analyses (31, 32).

Differences in comparisons within experiments, journal articles, and research groups can result in dependent effect sizes leading to narrow confidence intervals (CI) and small estimates of SE (33, 34). We completed multilevel modelling to account for such dependencies, with separate levels for comparisons within participant samples, experiments within studies, and studies within the same research group. As indicated by Akaike

information criteria and likelihood ration test results, the addition of each level did not improve model fit (Table S3).

Meta-analyses were performed using R (35) with the meta package (36). Due to the variability in study design and outcomes, random effects models were used. Effect sizes were interpreted as trivial ($g < 0.20$), small ($g = 0.20$), moderate ($g = 0.50$) or large ($g > 0.80$) (37). A negative effect size favors active tDCS, indicating that active protocols reduce the outcome measure. In comparison, positive effect sizes would indicate an increase in the measure following active versus sham tDCS, favoring sham tDCS. Effect size heterogeneity was assessed using the I^2 index, and interpreted as might not be important (0 to 40%), may represent moderate heterogeneity (30 to 60%), may represent substantial heterogeneity (50 to 90%), and may represent considerable heterogeneity (75 to 100%) (38). To test for publication bias, Egger's regression was used (39). Subgroup analyses were conducted to identify potential moderating effects of tDCS parameters on outcome measures. Where a meta-analysis was not possible, a systematic literature review is included.

3. RESULTS

In this section we provide the results of the review and discuss the findings. A total of 1,135 articles were identified, and after removing duplicates and assessing eligibility, 28 articles were included in the present review (Figure S1). All reviewed studies used conventional tDCS procedures and were sham-controlled trials, with 12 between-participant and 16 within-participant studies. A total of 996 participants were recruited across the reviewed studies, ranging from 9 to 172 individuals per study, and included individuals with healthy weight (n = 14 studies, 576 participants), overweight or obesity (n = 15 studies, 393 participants). Ljubisavljevic et al. (29) included individuals with healthy weight or overweight, but do not provide total n for each weight category.

Most studies recruited individuals classed as “healthy”, which refers to a lack of medical or behavioral conditions and is irrespective of weight status. A small number of studies recruited participants with specific conditions, such as Prader Willi Syndrome (40), Catechol-O-methyl transferase (COMT) Val158Met polymorphism (26, 27), frequent food cravings (6, 7, 41, 42), restrained eating (43, 44), binge eating disorder (45, 46), and anorexia or bulimia nervosa (47, 48). Heterogeneity across studies (I^2 range = 0 to 45%) suggests it might not be important (Table S4). Funnel plots show good symmetry across measures (Figure S4), with Egger’s regression suggesting little evidence of publication bias ($p > 0.08$). A summary of the meta-analytic data and forest plots are available in the Supplemental Digital Content.

3.1. Study Quality

Only 7 of the 28 studies showed low risk of bias across all domains, and therefore an overall low risk of bias. Across the remaining studies, insufficient detail around participants and researcher blinding was the greatest source of bias, particularly the process in which researcher blinding was upheld. This also affected risk of bias judgement for the measurement of outcome and selection of reported results. Most studies (n = 18) maintained a double-blind protocol, either through the use of a pin-protected stimulation device or an independent researcher completing stimulation protocols. Seven studies used a single-blind design, with a further three studies providing insufficient detail around blinding protocols.

Additional bias arose due to the post-randomization exclusion of participants (n = 14 studies). Many studies do not provide a sample size calculation, which makes it difficult to identify the impact of these exclusions. The exclusion of participants is particularly problematic where this leads to a relatively small sample size, which is an important consideration due to the repeated use of small sample size across tDCS research (14, 49, 50). Ray et al. (30) included a source of intended bias around participant blinding, with the aim of assessing the impact of expecting to receive active versus sham tDCS on eating-related measures. Although this study received an overall high risk of bias, the study was

high-quality and this source of bias provides important considerations around the information shared with participants. The RoB assessment is summarized in the Supplemental Digital Content (Figures S2 and S3).

3.2. Montage

The most common target location is the right dorsolateral prefrontal cortex (DLPFC) (n = 17), with a smaller proportion of studies targeting the left DLPFC (n = 8) (Table 2). This cortical region is of interest due to its role in executive functioning, a process associated with the control of reward-driven appetite through the increase in inhibitory control and curbing of impulsive behaviors (51, 52). Where the anode was placed over the right DLPFC and cathode over the left DLPFC, a reduction across measures was seen (*g* = -0.39 to 0.01) (Figures S5 to S10). Less consistent patterns were found when both anode and cathode electrodes are placed over alternative cortical regions, although effect sizes are often based only on single studies (Figures S5 to S10; Table S2). The right DLPFC is of particular interest as reduced activity of this region is associated with poor control of dietary behaviors and obesity (53). The consistent negative effect sizes across eating-related measures when targeting the right DLPFC may lend support for this right brain hypothesis of obesity (53).

**** INSERT TABLE 2 HERE ****

Many studies delivering tDCS across other cortical regions also measured effects when targeting the right DLPFC. Composite scores were calculated for these studies, to retain one effect size per participant group and avoiding increasing homogeneity (31), and as such were removed from analyses. However, the results of these studies provide further support for targeting the right DLPFC. For example, Carvalho et al. (54) found increased preference for chocolate following anode left/cathode right DLPFC stimulation, when compared with both anode right/cathode left DLPFC and sham protocols. The authors also found craving

intensity was reduced to a greater extent by anode right/cathode left montages compared with anode left/cathode right DLPFC stimulation; replicating findings by Fregni et al. (6).

Further studies targeting the left DLPFC failed to identify a change in measures of subjective appetite, food craving or food consumption (26, 27). Additionally, Marron et al. (55) found increased hunger and desire to eat when applying 2.0 milliampere (mA) for 20 minutes with the anode over the left DLPFC and cathode over the cerebellum. Targeting the left DLPFC appears to have minimal effect on eating-related measures and suggests greater importance for targeting the right versus left DLPFC, providing further support for the right brain hypothesis (53). However, not all studies have found an effect of tDCS when applied to the right DLPFC (Figures S5 to S10). This may be due to the eating behavior traits of the recruited participants, with these studies recruiting individuals who do not display a susceptibility to overconsumption and are likely able to appropriately inhibit impulsive behaviors through effective executive control. In comparison, an effect is more consistently shown in those with frequent food cravings or binge-type behaviors (6, 7, 41, 42, 45, 46). This highlights a potential behavior trait-dependent effect of tDCS (56).

Novel target locations include the right inferior frontal gyrus (IFG) (43, 44), medial prefrontal cortex (PFC) (48), right extrastriate body area (EBA) (48), and the primary motor cortex representation of the tongue muscle (tnM1) (57) (Figure 1). These regions are additionally associated with consumptive behaviors, however data following the use of these more novel montages show no significant stimulation effects or an increase in measures of food consumption and implicit preference (44, 48). The IFG and medial PFC are in anatomically close proximity to the DLPFC, and the large electrodes used in these studies are likely to overlap the DLPFC. However, these alternative montages likely change the current distribution when compared to DLPFC-targeted stimulation (58). The effects of tDCS may be dependent on the current entering the DLPFC, specifically the right hemisphere, and so the small amount of current potentially entering through close proximity with an alternative target

region may be insufficient to cause any meaningful modulation. This further suggests the DLPFC is an important focal target for the modulation of eating behaviors.

**** INSERT FIGURE 1 HERE ****

In addition to variation in target location, researchers opt for different reference electrode locations. Across the included studies, the reference electrode was placed bilaterally to the target electrode (i.e., over the same cortical region, but on the opposite hemisphere; e.g., right and left DLPFC), over the contralateral supraorbital region (i.e., above the eye on the opposite hemisphere; e.g., right DLPFC and left supraorbital region), or over the occipital lobe or cerebellum (Figure 1). A comparison of the potential effects of different reference electrode positions on eating behaviors has not been conducted, and it is difficult to fully identify any potential impacts. Moving the reference electrode to alternative locations is likely to alter the current distribution, and may affect the expected tDCS-induced effects (58, 59). While there are similar reductions in eating-related measures when comparing tDCS with the same target location but differing reference electrode positions (e.g., left DLPFC versus left supraorbital region) (6, 7, 40-42, 45, 60), there was variation in effect sizes (Table S2). Again, these analyses should be interpreted with caution as the overall effect sizes are often based on single-studies and are likely driven by other variables.

One way to minimize the physiological impact of the reference electrode is to place it over an extracephalic region, that is over a region of the body that is not the cortex (61). One study placed the reference electrode over the contralateral cheek (43), and three studies placed this electrode on a section of the participant’s arm or shoulder (10, 29, 46). The advantage of these extracephalic montages is that the physiological effects of the reference electrode are minimized (62, 63), however this may be at the expense of altering the direction and distribution of the electric current (14, 61). Despite these effects, placing the reference electrode over an extracephalic region did not appear to impact the effects of tDCS on

behavioral measures as observed when using cephalic montages, with comparable effect sizes following cephalic versus extracephalic montages (Table S2; Figures S11 to S16).

3.3. Current Intensity and Current Density

The most consistently applied current intensity is 2.0 mA, delivered across 23 of the 28 studies. One study applied 1.5 mA (43), and 5 studies delivered 1.0 mA (9, 46, 48, 57, 60). It has been suggested that 2.0 mA is the minimum intensity required to elicit changes in eating-related measures (17, 32). However, since the publication of these papers, Chen et al. (43) applied 1.5 mA and found improved reaction times in a stop-signal task. This intensity warrants further investigation, especially in light of the potential issues surrounding blinding efficacy at higher current intensities (64) (see 3.5). Unlike the earlier meta-analyses, the present analysis found comparable effects of differing current intensities when incorporating more recently published work (Figures S17 to S22).

It could be that, rather than current intensity, the effects of tDCS are driven more by the density of applied current (i.e., the amount of current delivered per unit area [$mA \cdot cm^{-2}$]), as low current densities will likely diminish the effect of stimulation on the underlying cortex (3). The suggested minimum intensity of 2.0 mA equates to a minimum current density between 0.057 and 0.080 $mA \cdot cm^{-2}$, in line with commonly used electrode sizes of 25 and 35 cm^2. Indeed, this appears to be the boundary within which tDCS is able to modulate measures of eating behavior (Figures S23 to S28). In particular, 0.057 $mA \cdot cm^{-2}$ resulted in a consistent reduction (i.e., favoring active tDCS) across all measures (g = -0.25 to -0.06). As comparable current densities are achieved through varying current intensities and electrode sizes, this may explain why we were unable to replication the intensity-dependent effect (17).

Maintaining a comparable current intensity, and therefore current density, does not occur in all studies. Four studies applied 1.0 mA using large 35 cm^2 electrodes, resulting in a current

density of 0.029 $mA \cdot cm^{-2}$ (9, 46, 57, 60). These studies failed to find an effect of stimulation across measures of hunger and food craving, with the exception of Jauch-Chara et al. (60) who identified reduced food consumption following repeated sessions of active tDCS, potentially due to a cumulative effect (60) (see 3.7).

3.4. Stimulation Duration

Stimulation was applied for 15 minutes (n = 1), 20 minutes (n = 23), 30 minutes (n = 3), and 40 minutes (n = 2) across the reviewed studies. Vicario et al. (57) delivered 15 minutes of 1.0 mA stimulation to the left tnM1, which failed to change subjective hunger scores. All studies that used stimulation durations greater than 20 minutes also used multi-session protocols, where tDCS was delivered over subsequent days (10, 25-27, 40) (see 3.7). Comparison of effects following single-session tDCS as part of these multi-session designs is largely not reported, and so the effects of longer stimulation durations in a single-session design cannot be made. Such extended durations should be used with caution, as data from motor cortex stimulation suggests that longer durations may lead to a reversal of the expected effect (65, 66). There are no recorded studies to date that have compared the effects of stimulation duration on eating behavior outcomes, and further studies utilizing shorter (10 to 15 minutes) durations are required as this would reduce the time requirement of participants.

3.5. Sham Protocols and Blinding

Commonly applied sham protocols involve the current being ramped up to the desired intensity and then delivered for 0 to 120 seconds before being ramped down (Figure 2). To imitate both the incremental and decremental currents integral to active tDCS protocols, some studies deliver the aforementioned ramping protocol at the start and end of the stimulation period. The common cutaneous sensations associated with delivery of the direct current typically occur at the start of current delivery (i.e., the ramp period) and often habituate within the initial seconds of stimulation (67). Therefore, sham protocols are

considered effective methods of participant blinding as they mimic the initial phase of active tDCS, but are unlikely to result in lasting modulation of the cortex due to the short duration (67-69). Although standardized sham protocols are generally assumed to be effective, researchers may struggle to maintain blinding at higher current strengths due to the more pronounced cutaneous sensations (64).

**** INSERT FIGURE 2 HERE ****

Only 12 studies included quantitative data on the effectiveness of sham protocols, with participants' ability to correctly guess the condition received ranging from 17 to 97% (Cohen's *d* = 0.33 to 0.58). Of these studies, participants were unable to identify active stimulation above the level of chance across 6 studies (9, 10, 29, 47, 54, 70). Many of these studies utilized 2.0 mA, suggesting that participant blinding can be achieved at higher current strengths. Two further studies report successful participant blinding, but do not provide data to support this (25, 42). The remaining studies reported failure to achieve adequate participant blinding, with correct guesses ranging from 60 to 97% (7, 8, 43, 44, 46, 48). Again, these studies oppose the notion that higher current intensities result in poorer participant blinding, as they include 1.0 and 1.5 mA protocols.

Based on the overall correct guess rate (i.e., number of participants able to identify active and sham protocols), there are considerable differences in effect sizes when comparing successful and unsuccessful blinding protocols. Where blinding was upheld, trivial-to-small positive effect sizes were observed (*g* = 0.05 to 0.31) (Figures S29 to S34). In comparison, studies with unsuccessful tDCS blinding resulted in more consistent negative effect sizes, particularly across measures of explicit wanting, food craving and hunger (*g* = -0.16 to -0.11) (Figures S29 to S34). Fassi and Cohen Kadosh (71) suggest, rather than focusing on overall correct guess rate, we should instead assess active guess rate (i.e., percentage of participants able to correctly guess receiving active protocols). The authors argue that

overall correct guess rate can lead to misleading estimate of blinding success (72). Across the reviewed literature, overall correct guess rate suggests participant blinding may be upheld (mean 48%, range 17 to 79%) whereas active guess rate demonstrates that participants are consistently able to identify active protocols (mean 73%, range 60 to 85%).

In addition, the effects of researcher blinding cannot be ignored. When comparing the effects of single- and double-blind study designs on tDCS modulation of eating behavior, variation in effect sizes is evident (Figures S35 to S40). In particular, the reduction in food consumption and explicit wanting following tDCS appear to be driven by studies utilizing single-blind design. Discrepancy in effect sizes further emphasizes the importance of implementing and maintaining a double-blind study design.

3.6. Offline versus Online Protocols

Offline protocols typically involve the participant remaining seated and relaxed with tDCS delivered without distraction. In comparison, online protocols employ specific tasks during the stimulation period, such as cognitive training (14). Many of the studies in this review used offline protocols (n = 20). Eight studies applied online tDCS, where participants watched unrelated media (e.g., nature documentary, cartoon) (10, 48), completed a food-related task (e.g., food choice computer-based task) (7, 9, 46, 73), or completed a cognitive task (e.g., approach-avoidance training, Go/No-Go task) (8, 54). Variation in effect sizes is evident when comparing offline and online protocols (Figures S41 to S46). Where offline protocols produce a more consistent trivial-to-small negative effect size (g = -0.31 to 0.12), with the exception of hunger measures, there is greater variation in the effects following online protocols (g = -0.16 to 0.15).

3.7. Number of Stimulation Sessions

A total of 9 studies included repeated sessions of active or sham tDCS, ranging from 3 to 16 sessions. These multi-session studies appeared to result in a cumulative effect, with small

effect sizes for measures of food craving (*g* = -0.29; 95% CI = -0.60 to 0.03) and food consumption (*g* = -0.34; 95% CI = -1.03 to 0.35), compared to only trivial effect sizes following single session tDCS (*g* = -0.08 to 0.01) (Figure 3).

**** INSERT FIGURE 3 HERE ****

4. Discussion

The findings of the review related to specifics of the studies and relevant parameters are discussed above. In this section, we provide a general discussion of the findings with further consideration of specific parameters. In this review we have considered the impact of a range of stimulation parameters, and what methodological issues may explain the observed inconsistencies in data. Figure 4 captures the variation in applied tDCS parameters across the reviewed research. While our meta-analyses were unable to capture all parameter variation, they have identified parameters that appear to modulate eating behavior. We argue that a more holistic and comprehensive consideration of these parameters is required to identify a consistent effect of tDCS protocols on eating-related measures. In Table 3 we propose a range of tDCS parameters that appear to be most effective for modulating eating behaviors. This is not intended as an absolute recommendation, but as a point of reference and to help further discuss the most effective parameters for eating-related studies. In addition to these, researchers should adhere to a double-blind protocol with a within-participant (randomized and counterbalanced) design, particularly for single-session studies and where this fits the study aims. We also suggest that studies provide sufficient detail on the study design and implemented tDCS parameters so the effects of parameter sets can be fully understood. Protocols using parameters known to affect the outcome, such as online tasks, should be carefully considered with a clear justification for their use.

**** INSERT FIGURE 4 HERE ****

**** INSERT TABLE 3 HERE ****

As discussed above, current density may be a more important driver of tDCS effects than current intensity. Lower current intensities, such as 1.0 mA, can be utilized whilst maintaining current densities in line with 2.0 mA protocols. For example, for 1.0 mA protocols the electrode size can be reduced to between 12.5 and 17.5 cm^2, resulting in current densities between 0.057 and 0.080 $mA \cdot cm^{-2}$. It should be noted that increasing the current density is unlikely to lead to linear effects on the underlying cortex and outcome measures, but greater current densities may provide more consistent effects (61, 74). Animal models suggest tissue damage occurs at current densities above 25 $mA \cdot cm^{-2}$ (75); to maintain participant safety, current density should not exceed this threshold (76).

When considering the specific tDCS parameters, and the potential impact these may have on behavior, the reference electrode should not be ignored as it is probable that this electrode exerts some physiological effect on the cortex which will likely affect outcome measures (3, 58). Therefore, careful consideration of the placement of both electrodes is required, with the reference electrode placed over a region unrelated to the outcome measure (14). It is assumed that increasing the distance between electrodes results in a greater amount of the current entering the brain, as opposed to being shunted across the scalp (58). However, many studies place the target and reference electrodes relatively close together, such as bilaterally over the DLPFC (6, 7).

The effect of increasing electrode distance on measures of eating behavior is not clear. The ability of extracephalic montages to increase the amount of current penetrating deeper brain structures is also unclear (77, 78), although they do appear able to reduce the amount of current being shunted across the scalp (61, 79). If extracephalic montages are able to increase the amount of current reaching deeper brain structures, this may be important for reaching those structures involved in rewarding components of eating behavior, such as the nucleus accumbens (80). Further research that includes neuroimaging techniques is needed

to support this premise. If an extracephalic montage is used, there should be careful consideration of other parameters; for example, higher current intensities may be required to compensate for the greater distance between electrodes (81).

Reflecting on the issues raised with reference electrode placement (see 3.20), any modulatory effect of the reference electrode may be diminished by using a large electrode size. Electrodes are typically equal size of 25 or 35 cm^2, but range from 16 to 70 cm^2. When electrodes are equal size there is similar cortical neuromodulation (with opposite polarity) under both electrodes. In comparison, when the size of one electrode is increased, the current density is reduced under that electrode which results in modulation under the smaller electrode area only (82). Two studies have used larger reference electrodes (48, 70). Although these studies do not show improvements in eating-related measures, this again may be driven by methodological issues such as the use of an online task (48) (see 3.6). The use of large reference electrode size in eating behavior studies, especially with offline protocols, is yet to be fully determined. Large reference electrodes can alter the current distribution and may reduce the deleterious effects associated with the cathode (83). Increasing reference electrode size should be combined with the use of greater distances between electrodes, such as extracephalic montages, to minimize the chance of current shunting across the scalp (79, 84).

The effects of tDCS are brain state-dependent and can be shaped by the use of online protocols (3, 15). Offline protocols lead to modifications of cortical activity that last beyond the stimulation duration, whereas the use of online tasks leads to modulation of cortical activity related to the specific task (1, 85). Additionally, the use of an unrelated online task may impact the expected polarity-dependent effects of tDCS (14). This may explain the lack of expected effects on eating-related measures across the reviewed studies that use online protocols. Even where a food-based training task is used to modify food choice behavior, these studies typically measure wider eating-related measures such as food craving and

consumption (9, 73). Although food choice is an important driver of food consumption, food cravings are a more influential predictor of dietary intake and focusing on tasks promoting the regulation of food cravings may provide more fruitful effects (86)

It is currently unclear which participant populations may benefit from the use of online protocols (74, 87, 88), and many studies fail to sufficiently justify the use of these protocols. Where tDCS is delivered alongside a cognitive training task there appears to be improved performance relating to the specific task, which highlights the importance of employing an online task that is specific to the outcome measure of interest (88, 89). The impact of online tasks on the direction of stimulation effects and outcome measures warrants careful consideration of their use, but it may prove beneficial to use online protocols to enhance the modulatory effects of tDCS on specific eating-related measures. However, the online tasks performed in the reviewed studies are not always eating behavior-specific, and typically focus on improving cognitive functions (8, 54). This may lead to improvements in the cognitive measure, at the expense of improving eating behavior scores (85).

Gluck et al. (10) performed tDCS while participants watched nature or history documentaries and they were able to show reduced consumption of fats and soda when comparing anodal versus cathodal stimulation. This suggests the use of unrelated media with the aim diverting thoughts away from food may prove a valuable procedure for standardizing participants' thoughts during tDCS delivery. Until a clear effect of tDCS on eating behaviors is consistently reported or a clear impact of online protocols on eating-related measures can be identified, online protocols should be used with caution and a clear justification for their inclusion should be provided.

Across the reviewed studies, stimulation was typically applied daily, with four studies initially applying stimulation with a 24-hour interval and increasing this to 48 hours in the second stage of the study (e.g., from inpatient to outpatient treatment) (24-27). Although a 48-hour

interval is likely to negate the cumulative effects of stimulation (90), it is possible that increasing the interval to 48 hours following initial daily stimulation could strengthen the modulatory effects. However, studies that implement this protocol failed to identify any change in subjective appetite or food craving scores (24-27), but this may be due to their focus on left DLPFC stimulation or longer stimulation durations. This poses an important consideration for multi-session designs; whether daily sessions of stimulation are required, or if the number of sessions can be reduced later in the study to minimize the time requirements of participants. Again, further data are required to determine the impact of daily to second-daily stimulation protocols, which should adhere to effective parameters.

There appears to be the potential for repeated session to negate the deleterious effects when parameters are below the proposed effective range, as discussed in the above sections. For example, Jauch-Chara et al. (60) used low current intensity (1.0 mA) and density (0.029 $mA \cdot cm^{-2}$), but they were able to demonstrate an ability of anodal tDCS to reduce food consumption and subjective appetite following 8 sessions. This suggests that repeated low-level stimulation may lead to a cumulative improvement in eating-related measures, however there is not currently sufficient data to confirm this effect. If low-intensity stimulation is able to modulate eating behaviors across multiple sessions, this may produce a more consistent effect of tDCS than single-session stimulation but will require greater resources and commitment from potential participants. Multi-session designs should not come at the cost of appropriate stimulation parameters, and studies using single-session stimulation are still important for determining effective parameter ranges and the modulatory effect of tDCS on measures of eating behavior; they have also demonstrated significant effects on a number of occasions (6, 7, 28, 45).

Reflecting on our RoB assessment, the implementation and maintenance of participant and researcher blinding is the main source of bias across many of the reviewed studies. In particular, little detail is given around researcher blinding protocols in several studies. It is

likely that poor researcher blinding contributes to poor participant blinding, as ineffective researcher blinding can lead to several confounding factors such as expectation effects, protocol adjustments or biases in the analysis and reporting of data (91). Researcher blinding can be achieved through the use of pin-protected devices where the stimulation parameters are pre-set by an independent individual (e.g., (70)). To control for potential unblinding of researchers it is recommended that the efficacy of researcher blinding is measured.

Additionally, the greater prevalence of adverse events following active tDCS may reduce the ability to blind participants (92). However, this is of particular debate as not all studies find a difference in adverse events between active and sham conditions (68). Poor blinding may be driven by visual cues such as erythema (skin redness), which is more common following active stimulation (64). This visual discrepancy between active and sham protocols easily signifies to the participant and researcher that a difference between conditions exists and potentially which condition the participant has received (64, 93). Six studies report either greater erythema following active conditions or similar redness following active and sham protocols (10, 24, 25, 40, 60, 70). Three of these studies reported successful participant blinding, while also reporting no difference in skin redness (10, 25, 70), which suggests erythema may indeed be contributing to ineffective participant blinding (64, 93).

Participant blinding can be maintained by preventing the participant from observing their skin following stimulation. However, researcher blinding is less straight forward to uphold where visible differences are evident and this may account for some of the variation in data (94). Careful consideration of stimulation parameters and device set-up should be made to minimize the likelihood of erythema and maintain a double-blind design. Additionally, pre-treatment of the skin with dermatological products may reduce occurrence and severity of redness, but this may not be appropriate for all studies or participant groups (95). The impact

598 on current resistance by preparing the skin with these products is not well established, and
599 to account for any potential effects all preparatory steps must be recorded (11).
600
601 The information provided to participants should also be carefully controlled. Providing
602 information to participants that will lead to an expectation of effect will likely change scores,
603 resulting in an effect that is unrelated to the stimulation technique (30). Participants should
604 be given sufficient information to provide informed consent, but this should omit any study
605 hypotheses or expected effects of the study protocol. Answers provided to any participant
606 queries or comments made around the efficacy of tDCS should also be controlled. It should
607 be noted that individuals who have previously undergone or are knowledgeable of tDCS
608 procedures may be more likely to identify active protocols than tDCS-naïve individuals, and
609 so the inclusion of those who have previously undergone stimulation should be avoided to
610 maintain blinding efficacy (96).
611
612 Additional data are required to confirm some of the assumptions we have made, such as the
613 effective current density range, with further data required to determine the efficacy of some
614 parameters. We do not expect that all future studies will adhere to the parameters described
615 in this section, and it is important that further studies test the efficacy of parameters outside
616 these ranges. However, from the data included in this review, these appear to be the most
617 effective parameters for modulating eating-related outcomes. Whilst we acknowledge that
618 the present review does not extend to the discussion of physiological implications of differing
619 stimulation parameters, we have been able to describe those parameters that appear
620 effective on a behavioral level. The paucity of research describing the physiological effects of
621 tDCS remains problematic, ensuring it was not possible to fully discuss these implications in
622 this review. We encourage researchers to explore the physiological effects of differing tDCS
623 parameters to highlight the underpinning physiological mechanisms that drive the behavioral
624 effects we describe here.
625

5. CONCLUSION

The first study measuring the effects of tDCS on food craving and consumption was published more than a decade ago, and we are still at a relatively early stage in our understanding of the effects and potential role of this technique for the control of eating behavior. Interest in this area has proliferated over recent years, but many studies have employed varying study designs and stimulation parameters which makes it difficult to identify a consistent effect of tDCS. Careful consideration of stimulation parameters is important for all studies. This is not a new concept with many recent reviews highlighting the need for consistent and appropriate parameter use (3, 12, 14).

In this review, we have extended the discussion to incorporate a more comprehensive range of parameters and have outlined potentially effective ranges for these parameters. We acknowledge that some of the analyses, conclusions and assumptions we have made are based on a limited number of studies, which reflects the relative novelty of these studies. However, there is good evidence to support these conclusions from wider research, some of which we have included in this review. Initial variation in applied parameters is important for identifying the most appropriate parameters to apply. However, more consistency in parameter application is required in future work in order to fully understand the impact of tDCS and the efficacy of this technique to modulate the hedonic responses to food. This also highlights the need for publication of null effects and the use of Bayesian statistics, which can be used to identify those parameters, populations or measures that appear to be outside the modulatory influence of tDCS. The aim of this review was to identify effective parameter ranges, and through our discussion we hope to improve the quality of future studies through the application of appropriate study design and effective stimulation parameters. We also hope this will also lead to continued discussion around these considerations.

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657 **AUTHOR CONTRIBUTIONS**

658 **Jordan D. Beaumont**: Conceptualization, Methodology, Validation, Investigation, Data
659 curation, Writing – original draft, Writing – review & editing, Visualization, Project
660 administration. **David Starr**: Validation, Data curation. **Natalie C. Smith**: Validation, Data
661 curation. **Danielle Davis**: Conceptualization, Writing – review & editing, Supervision.
662 **Michelle Dalton**: Conceptualization, Writing – review & editing, Supervision. **Alexander**
663 **Nowicky**: Writing – review & editing. **Mark Russell**: Writing – review & editing. **Martin J.**
664 **Barwood**: Conceptualization, Methodology, Validation, Writing – review & editing,
665 Supervision.
666

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957

FIGURE CAPTIONS

Figure 1 A comparison of cephalic montages; black circles represent target (left) or reference (right) electrode locations. Image adapted from Klem, Lüders (97).

Figure 2 A comparison between active and commonly applied sham protocols. In active tDCS, the current is ramped up to the desired intensity and delivered for several minutes before being ramped down and switched off. Sham protocols involve the current being ramped up to the desired intensity and then either immediately ramped down and turned off (Sham A), or delivered for several seconds before being ramped down (Sham B). Alternatively, one of these sham protocols is repeated at the end of the stimulation period to imitate both incremental and decremental currents integral to active tDCS protocols (Sham C).

Figure 3 Forest plots comparing single- and multi-session protocol across (a) food craving and (b) food consumption measures.

Figure 4 Summary of variation in tDCS parameters observed across the reviewed studies.

978 **Table 1** Literature search terms

Database	Search Terms
MEDLINE PsycINFO Scopus	(*"noninvasive brain stimulation" OR "non-invasive brain stimulation" OR "transcranial direct current stimulation" OR "transcranial current stimulation" OR tDCS) AND (appetit* OR food OR "food crav*" OR "food reward" OR "food preference*" OR "food cue" OR "food consumption" OR eat* OR calorie* OR "calorie intake" OR "calorie consumption" OR energy OR "energy intake" OR "energy consumption" OR bing* OR "binge eat*" OR snack**)
Science Direct	*("transcranial direct current stimulation" OR tDCS) AND ("food craving" OR "food reward" OR "food preference" OR "food consumption")*

979

980 **Table 2** Comparison of tDCS parameters across studies

		Montage[a,b]				Stimulation Duration			
	Intervention	Target Electrode	Reference Electrode	Electrode Size (cm^2)	Current Intensity (mA)	Ramp (seconds)	Active (minutes)	Sham (seconds)	Number of Stimulation Sessions
Amo Usanos et al. (2020) (24)	Anodal, Sham	F3	Right supraorbital	25	2.0	30	20	15 at start and end	8
Beaumont et al. (2021) (70)	Anodal, Sham	F4	Oz	25 / 51 [c]	2.0	30	20	36	1
Bravo et al. (2016) (40)	Anodal, Sham	F4	Left supraorbital	35	2.0	15	30	0 (ramp only)	5
Burgess et al. (2016) (45)	Anodal, Sham	F4	F3	Not reported	2.0	Not reported	20	120 at start, 60 at end	1
Carvalho et al. (2019) (54)	Anodal, Cathodal, Sham	F4	F3	35	2.0	15	20	15	1
Chen et al. (2019) (43)	Anodal, Sham	Right IFG (midpoint F4-F8)	Left cheek	25	1.5	30	20	0 (ramp only)	1
Fassini et al. (2019) (27)	Anodal, Sham	F3	Right supraorbital	25	2.0	30	30	30	16
Fassini et al. (2020) (26)	Anodal, Sham	F3	Right supraorbital	25	2.0	30	30	30	16

(Table 2 continued)

Fregni et al. (2008) (6)	Anodal, Cathodal, Sham	F3 / F4	F4 / F3	35	2.0	Not reported	20	30	1
Georgii et al. (2017) (9)	Anodal, Sham	F4	F3	35	1.0	15	20	15	1
Gluck et al. (2015) (10)	Anodal, Cathodal, Sham	F3	Left forearm / Right supraorbital	25	2.0	30	40	15	3
Goldman et al. (2011) (7)	Anodal, Sham	F4	F3	Not reported	2.0	30	20	60	1
Grundeis et al. (2017) (73)	Anodal, Cathodal, Sham	F8	Af7	35	2.0	30	20	0 (ramp only)	1
Heinitz et al. (2017) (25)	Anodal, Sham	F3	Right supraorbital	35	2.0	Not reported	40	10	15
Jauch-Chara et al. (2014) (60)	Anodal, Sham	Right DLPFC	Left supraorbital	35	1.0	8	20	0 (ramp only)	8
Kekic et al. (2014) (42)	Anodal, Sham	F4	F3	25	2.0	10	20	30	1
Kekic et al. (2017) (47)	Anodal, Cathodal, Sham	F4	F3	25	2.0	10	20	30	1

(Table 2 continued)

Lapenta et al. (2014) (41)	Anodal, Sham	F4	F3	35	2.0	15	20	30	1
Ljubisavljevic et al. (2016) (29)	Anodal, Sham	F4	Left forearm	35	2.0	30	20	0 (ramp only)	5
Marron et al. (2019) (55)	Anodal, Sham	F3	Right cerebellum	25	2.0	Not reported	20	Not reported	1
Mattavelli et al. (2019) (48)	Anodal, Sham	Midpoint Fz-F3 / O2-PO8	Contralateral supraorbital	16 / 35 [c]	1.0	10	20	40 at start, 30 at end	1
Max et al. (2020) (46)	Anodal, Sham	F4	Left deltoid muscle	35	1.0 / 2.0	5	20	46	1
Montenegro et al. (2012) (28)	Anodal, Sham	F3	Fp2	35	2.0	Not reported	20	30	1
Ray et al. (2017) (98)	Anodal, Sham	F4	F3	24	2.0	Not reported	20	Not reported	Not reported
Ray et al. (2019) (30)	Anodal, Sham	F4	F3	24	2.0	Not reported	20	60 at start and end	Not reported
Sedgmond et al. (2019) (8)	Anodal, Sham	F4	F3	35	2.0	10	20	30	1
To et al. (2018) (44)	Anodal, Sham	Right IFG (midpoint F4-F8)	Midpoint F3-F7	25	2.0	30	20	0 (ramp only)	Not reported

(Table 2 continued)

Vicario et al. (2020) (57)	Anodal, Cathodal, Sham	Left tnM1	Right mastoid process	35	1.0	30	15	0 (ramp only)	1

Af7, anterior frontal area 7; DLPFC, dorsolateral prefrontal cortex; F3, frontal area 3; F4, frontal area 4; F7, frontal area 7; F8, frontal area 8; Fp2, fronto-polar area 2; Fz, frontal zero point; IFG, inferior frontal gyrus; mA, milliampere; O2, occipital area 2; Oz, occipital zero point; PO2, parieto-occipital area 2; tnM1, area of primary motor cortex representing the tongue muscle

[a] *See Klem et al. (1999) (97).*

[b] *All sham protocols used the same montage as active protocols.*

[c] *Target electrode size / reference electrode size*

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982 **Table 3** Proposed Effective tDCS Parameters

Montage	Target: Right DLPFC Reference: Cortical region away from DLPFC, or extracephalic region
Electrode Size	Target: ≤35 cm^2 Reference: Equal or greater than target electrode
Current Intensity	1.5 – 2.0 mA
Current Density	0.057 – 0.080 $mA \cdot cm^{-2}$
Stimulation Duration	20 minutes
Inter-session Interval	Single-session: >48 hours Multi-session: ≤24 hours
Offline / Online Protocol	Offline; Unrelated media used as an online task may be appropriate for standardizing participants' thoughts during stimulation

983

Supplemental Digital Content

Table S1 PRISMA checklist.

Table S2 Summary of meta-analytic data.

Table S3 Output of multi-level modelling.

Table S4 Summary of heterogeneity and publication bias data across eating-related measures.

Figure S1 PRISMA flow diagram detailing the search and selection process performed to identify studies applying tDCS for the modulation of eating behaviors.

Figure S2 Overall risk of bias across the 28 reviewed studies.

Figure S3 Risk of bias assessment within studies.

Figure S4 Contour-enhanced funnel plots across eating-related measures.

Figures S5 to S10 Forest plots comparing montages.

Figures S11 to S16 Forest plots comparing cephalic versus extracephalic montages.

Figures S17 to S22 Forest plots comparing current intensities.

Figures S23 to S28 Forest plots comparing current densities.

Figures S29 to S34 Forest plots comparing blinding success.

Figures S35 to S40 Forest plots comparing single- versus double-blind protocols.

Figures S41 to S46 Forest plots comparing online versus offline protocols.