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

3

4 **Running title:** Effective tDCS parameters for eating behavior

5

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18

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25 **ABSTRACT**

26 *Objective*

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

30

31 *Methods*

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

38

39 *Results*

40 We identified 28 eligible studies; seven showed low risk of bias, with the remaining studies
41 showing bias arising from issues implementing or reporting blinding protocols. Large
42 variation in applied parameters was found, including montage, current intensity and density,
43 participant and researcher blinding, and the use of online or offline tasks. The application of
44 differing parameters appeared to alter the effects of tDCS on eating-related measures,
45 particularly for current density ($g = -0.25$ to 0.31), and when comparing single-session ($g = -$
46 0.08 to 0.01) versus multi-session protocols ($g = -0.34$ to -0.29). Some parameters result in
47 null effects.

48

49 *Conclusion*

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

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

55

56 **KEYWORDS**

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

59

60 **ACRONYMS**

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

68

69 1. INTRODUCTION

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

83

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

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

100

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

111

112 **2. METHODS**

113 ***2.1. Search Strategy***

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

122

123

*** INSERT TABLE 1 HERE ***

124

125 **2.2. Inclusion and Exclusion Criteria**

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

138

139 **2.3. Data Extraction**

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

145

146 **2.4. Study Quality Assessment**

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

151

152 **2.5. Meta-Analysis**

153 Means, standard deviations (SD) and sample size were extracted for eating-related
154 measures. Where standard error (SE) was reported, SD was estimated using the equation
155 $SD = SE \times \sqrt{n}$ (20). If data were not reported, datasets were requested from corresponding
156 authors. Otherwise, means and SD or SE were extracted from available figures using
157 WebPlotDigitizer (version 4.4) (22), or estimated using the Practical Meta-Analysis Effect
158 Size Calculator (23) by entering t or F statistic and sample size. If data or effect sizes were
159 estimated, these were validated by two authors independently (JDB and NCS). Standardized
160 mean differences were calculated and adjusted using Hedges' g due to small sample size (n
161 < 20) across many of the reviewed articles.

162

163 Analyses focused on single-session tDCS, to remove the potential cumulative effect of multi-
164 session protocols. Four studies did not measure the effects of single-session tDCS and were
165 removed from analyses (24-27). Additional studies were removed due to missing data (28)
166 or due to all participants receiving active tDCS (29). To reduce confounding analyses, the
167 expectation effect observed by Ray et al. (30) was also removed. A total of 21 studies ($n =$
168 743 participants) were included in the meta-analysis (Table S5). Where possible, separate
169 analyses comparing single- versus multi-session tDCS were completed to identify any
170 cumulative effect (additional $n = 3$ studies, 105 participants). Where effect sizes are based
171 on composite scores (i.e., mean scores across varying levels of a specific parameter) within
172 the same participant group, these were removed from analyses for the specific parameter
173 measure to avoid confounding analyses (31, 32).

174

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

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

182

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

195

196 **3. RESULTS**

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

206

207 Most studies recruited individuals classed as “healthy”, which refers to a lack of medical or
208 behavioral conditions and is irrespective of weight status. A small number of studies
209 recruited participants with specific conditions, such as Prader Willi Syndrome (40), Catechol-
210 O-methyl transferase (COMT) Val158Met polymorphism (26, 27), frequent food cravings (6,
211 7, 41, 42), restrained eating (43, 44), binge eating disorder (45, 46), and anorexia or bulimia
212 nervosa (47, 48). Heterogeneity across studies (I^2 range = 0 to 45%) suggests it might not
213 be important (Table S4). Funnel plots show good symmetry across measures (Figure S4),
214 with Egger’s regression suggesting little evidence of publication bias ($p > 0.08$). A summary
215 of the meta-analytic data and forest plots are available in the Supplemental Digital Content.

216

217 **3.1. Study Quality**

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

226

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

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

238

239 **3.2. Montage**

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

252

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

254

255

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

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

265

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

279

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

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

293

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

295

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

310

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

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

321

322

323 **3.3. Current Intensity and Current Density**

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

333

334 It could be that, rather than current intensity, the effects of tDCS are driven more by the
335 density of applied current (i.e., the amount of current delivered per unit area [$\text{mA}\cdot\text{cm}^{-2}$]), as
336 low current densities will likely diminish the effect of stimulation on the underlying cortex (3).

337 The suggested minimum intensity of 2.0 mA equates to a minimum current density between
338 0.057 and 0.080 $\text{mA}\cdot\text{cm}^{-2}$, in line with commonly used electrode sizes of 25 and 35 cm^2 .

339 Indeed, this appears to be the boundary within which tDCS is able to modulate measures of
340 eating behavior (Figures S23 to S28). In particular, 0.057 $\text{mA}\cdot\text{cm}^{-2}$ resulted in a consistent
341 reduction (i.e., favoring active tDCS) across all measures ($g = -0.25$ to -0.06). As
342 comparable current densities are achieved through varying current intensities and electrode
343 sizes, this may explain why we were unable to replication the intensity-dependent effect (17).

344

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

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

351

352 **3.4. Stimulation Duration**

353 Stimulation was applied for 15 minutes (n = 1), 20 minutes (n = 23), 30 minutes (n = 3), and
354 40 minutes (n = 2) across the reviewed studies. Vicario et al. (57) delivered 15 minutes of
355 1.0 mA stimulation to the left tnM1, which failed to change subjective hunger scores. All
356 studies that used stimulation durations greater than 20 minutes also used multi-session
357 protocols, where tDCS was delivered over subsequent days (10, 25-27, 40) (see 3.7).

358 Comparison of effects following single-session tDCS as part of these multi-session designs
359 is largely not reported, and so the effects of longer stimulation durations in a single-session
360 design cannot be made. Such extended durations should be used with caution, as data from
361 motor cortex stimulation suggests that longer durations may lead to a reversal of the
362 expected effect (65, 66). There are no recorded studies to date that have compared the
363 effects of stimulation duration on eating behavior outcomes, and further studies utilizing
364 shorter (10 to 15 minutes) durations are required as this would reduce the time requirement
365 of participants.

366

367 **3.5. Sham Protocols and Blinding**

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

375 considered effective methods of participant blinding as they mimic the initial phase of active
376 tDCS, but are unlikely to result in lasting modulation of the cortex due to the short duration
377 (67-69). Although standardized sham protocols are generally assumed to be effective,
378 researchers may struggle to maintain blinding at higher current strengths due to the more
379 pronounced cutaneous sensations (64).

380

381

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

382

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

393

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

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

407

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

414

415 **3.6. Offline versus Online Protocols**

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

427

428 **3.7. Number of Stimulation Sessions**

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

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

434

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

436

437 **4. Discussion**

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

456

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

458

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

459

460 As discussed above, current density may be a more important driver of tDCS effects than
461 current intensity. Lower current intensities, such as 1.0 mA, can be utilized whilst maintaining
462 current densities in line with 2.0 mA protocols. For example, for 1.0 mA protocols the
463 electrode size can be reduced to between 12.5 and 17.5 cm², resulting in current densities
464 between 0.057 and 0.080 mA·cm⁻². It should be noted that increasing the current density is
465 unlikely to lead to linear effects on the underlying cortex and outcome measures, but greater
466 current densities may provide more consistent effects (61, 74). Animal models suggest
467 tissue damage occurs at current densities above 25 mA·cm⁻² (75); to maintain participant
468 safety, current density should not exceed this threshold (76).

469

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

479

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

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

490

491 Reflecting on the issues raised with reference electrode placement (see 3.20), any
492 modulatory effect of the reference electrode may be diminished by using a large electrode
493 size. Electrodes are typically equal size of 25 or 35 cm², but range from 16 to 70 cm². When
494 electrodes are equal size there is similar cortical neuromodulation (with opposite polarity)
495 under both electrodes. In comparison, when the size of one electrode is increased, the
496 current density is reduced under that electrode which results in modulation under the smaller
497 electrode area only (82). Two studies have used larger reference electrodes (48, 70).

498 Although these studies do not show improvements in eating-related measures, this again
499 may be driven by methodological issues such as the use of an online task (48) (see 3.6).

500 The use of large reference electrode size in eating behavior studies, especially with offline
501 protocols, is yet to be fully determined. Large reference electrodes can alter the current
502 distribution and may reduce the deleterious effects associated with the cathode (83).

503 Increasing reference electrode size should be combined with the use of greater distances
504 between electrodes, such as extracephalic montages, to minimize the chance of current
505 shunting across the scalp (79, 84).

506

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

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

518

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

530

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

539

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

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

552

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

567

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

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

578

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

590

591 Participant blinding can be maintained by preventing the participant from observing their skin
592 following stimulation. However, researcher blinding is less straight forward to uphold where
593 visible differences are evident and this may account for some of the variation in data (94).
594 Careful consideration of stimulation parameters and device set-up should be made to
595 minimize the likelihood of erythema and maintain a double-blind design. Additionally, pre-
596 treatment of the skin with dermatological products may reduce occurrence and severity of
597 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

626 **5. CONCLUSION**

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

635

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

651

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656

657 **AUTHOR CONTRIBUTIONS**

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659 curation, Writing – original draft, Writing – review & editing, Visualization, Project
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666

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957

958 **FIGURE CAPTIONS**

959

960

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

963

964 **Figure 2** A comparison between active and commonly applied sham protocols. In active
965 tDCS, the current is ramped up to the desired intensity and delivered for several minutes
966 before being ramped down and switched off. Sham protocols involve the current being
967 ramped up to the desired intensity and then either immediately ramped down and turned off
968 (Sham A), or delivered for several seconds before being ramped down (Sham B).

969 Alternatively, one of these sham protocols is repeated at the end of the stimulation period to
970 imitate both incremental and decremental currents integral to active tDCS protocols (Sham
971 C).

972

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

975

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

977

978 **Table 1** Literature search terms

Database	Search Terms
MEDLINE PsycINFO Scopus	<i>("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*)</i>
Science Direct	<i>("transcranial direct current stimulation" OR tDCS) AND ("food craving" OR "food reward" OR "food preference" OR "food consumption")</i>

979

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

	Intervention	Montage ^{a,b}			Current Intensity (mA)	Stimulation Duration			Number of Stimulation Sessions
		Target Electrode	Reference Electrode	Electrode Size (cm ²)		Ramp (seconds)	Active (minutes)	Sham (seconds)	
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 °	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
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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

982 **Table 3** Proposed Effective tDCS Parameters

Montage	Target: Right DLPFC Reference: Cortical region away from DLPFC, or extracephalic region
Electrode Size	Target: $\leq 35 \text{ cm}^2$ Reference: Equal or greater than target electrode
Current Intensity	1.5 – 2.0 mA
Current Density	0.057 – 0.080 mA·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

984 **Supplemental Digital Content**

985

986

987 **Table S1** PRISMA checklist.

988

989 **Table S2** Summary of meta-analytic data.

990

991 **Table S3** Output of multi-level modelling.

992

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

995

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

998

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

1000

1001 **Figure S3** Risk of bias assessment within studies.

1002

1003 **Figure S4** Contour-enhanced funnel plots across eating-related measures.

1004

1005 **Figures S5 to S10** Forest plots comparing montages.

1006

1007 **Figures S11 to S16** Forest plots comparing cephalic versus extracephalic montages.

1008

1009 **Figures S17 to S22** Forest plots comparing current intensities.

1010

1011 **Figures S23 to S28** Forest plots comparing current densities.

1012

1013 **Figures S29 to S34** Forest plots comparing blinding success.

1014

1015 **Figures S35 to S40** Forest plots comparing single- versus double-blind protocols.

1016

1017 **Figures S41 to S46** Forest plots comparing online versus offline protocols.

1018