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Incomplete evidence that increasing current intensity of tDCS boosts outcomes

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18 **Abstract**

19 **Background:** Transcranial direct current stimulation (tDCS) is investigated to modulate neuronal function
20 by applying a fixed low-intensity direct current to scalp.

21 **Objectives:** We critically discuss evidence for a monotonic response in effect size with increasing current
22 intensity, with a specific focus on a question if increasing applied current enhance the efficacy of tDCS.

23 **Methods:** We analyzed tDCS intensity does-response from different perspectives including biophysical
24 modeling, animal modeling, human neurophysiology, neuroimaging and behavioral/clinical measures.
25 Further, we discuss approaches to design dose-response trials.

26 **Results:** Physical models predict electric field in the brain increases with applied tDCS intensity. Data from
27 animal studies are lacking since a range of relevant low-intensities is rarely tested. Results from imaging
28 studies are ambiguous while human neurophysiology, including using transcranial magnetic stimulation
29 (TMS) as a probe, suggests a complex state-dependent non-monotonic dose response. The diffusivity of
30 brain current flow produced by conventional tDCS montages complicates this analysis, with relatively few
31 studies on focal High Definition (HD)-tDCS. In behavioral and clinical trials, only a limited range of
32 intensities (1-2 mA), and typically just one intensity, are conventionally tested; moreover, outcomes are
33 subject brain-state dependent. Measurements and models of current flow show that for the same applied
34 current, substantial differences in brain current occur across individuals. Trials are thus subject to inter-
35 individual differences that complicate consideration of population-level dose response.

36 **Conclusion:** The presence or absence of simple dose response does not impact how efficacious a given
37 tDCS dose is for a given indication. Understanding dose-response in human applications of tDCS is needed
38 for protocol optimization including individualized dose to reduce outcome variability, which requires
39 intelligent design of dose-response studies.

40 **Key Words:** Transcranial direct current stimulation (tDCS), Dose-response, Neuromodulation, Dose-
41 control

42 **Highlights:**

- 43 • Animal models show neuromodulation by single low-intensity electric fields, but no
44 comprehensive evidence for a linear dose-response relationship across tDCS relevant electric field
45 intensities.
- 46 • Clinical neurophysiology and imaging shows neuromodulation by tDCS but complex, state-
47 dependent none-monotonic changes with tDCS intensity. These experimental measures, along with
48 clinical and behavioral studies suggest significant inter-individual difference.
- 49 • We describe how assuming a causal chain across different scales (from single cells to local and
50 large networks to behavior) the lack of a linear response at any single scale may preclude an
51 aggregate linear dose response at the behavioral level.
- 52 • Despite ongoing advances in the science of tDCS, we currently do not have a clear understanding
53 of dose-response relationships in tDCS. Even as this knowledge develops, methods to normalize
54 tDCS dose across individuals are warranted.

55

56 **Introduction**

57 tDCS involves low-intensity direct currents (few mA) applied to the scalp via pad electrodes
58 (typically 25–35 cm^2) [1] or smaller electrodes in arrays (HD tDCS; [2]). Encouraged by the general safety
59 profile [3-5], low intensity tDCS has been broadly tested as a tool for cognitive research in healthy subjects
60 [6] as well as to treat a broad range of neurological and psychiatric disorders and symptoms [7, 8]. It is
61 generally accepted that the physics of tDCS dictates that current flow intensity in the brain (electric field)
62 will increase linearly with applied current (Figure 1) [9]. Rather, our primary question is whether
63 neurophysiological and behavioral responses also increase linearly, or at least monotonically, with applied
64 current intensity. Specifically, does increasing the current of tDCS (e.g. from 1 to 2 mA) increase effects
65 size for a given experiment and outcome measure? This question is relevant because any choice of

66 stimulation protocol and comparison among studies with different protocols rests on the ability to relate the
67 effects of one intensity to another in a rational way.

68 However, the question is complicated because the complete dose of tDCS is defined by the applied
69 current, the duration, and the electrode montage [10] which produce a complex pattern of current flow in
70 the brain; nonetheless, we focus here on the role of applied current intensity while noting how other factors
71 may influence (interact with) the current-intensity dose response. We discuss how individual anatomical
72 differences in the amount of current density (electric field) to the brain vary for the same applied current,
73 which may therefore lead to variations in individual intensity-response [11]. Moreover, we consider the
74 extent to which tDCS responses vary with brain-state, magnifying individual- and task specific variations
75 in dose-response.

76 In the last two decades, tDCS dose-response relationship has been evaluated from different
77 perspectives ranging from single cells, to small local brain circuits and synapses, to large networks, to
78 overall brain function and behavior. Assuming a causal chain across different scales (applied current first
79 changes single cells, which alter local and large networks, which change behavior), the lack of a linear
80 response at any of these scales may preclude an aggregate linear dose response at the behavioral level
81 (Figure 1). The organization of this document centers around measurement approaches (e.g. animal models,
82 imaging) but specific techniques often map specific scales (Figure 1; e.g. animal models measures small
83 circuits, imaging measures large network). We discuss tDCS intensity dose response through these different
84 perspectives.

85 **Basic biophysics of intensity-response**

86 Modeling studies relate the applied dose to the scalp [10], including current intensity, to the
87 resulting electric field (or current density) in the brain [12]. While current (in units of mA) is the controllable
88 stimulation parameter, electric field (in unit of V/m) reflects the local stimulation intensity each brain region
89 is actually exposed to. It is generally accepted that the physics of tDCS dictates that current flow intensity

90 in the brain (electric field) will increase linearly with applied current [9]. Therefore, the question is not if
91 there is a linear response between increasing applied current and brain electric field but rather if the brain
92 response to increasing electric field is itself linear. As noted above, in humans, the electric field varies with
93 individual anatomy (the implications of which are discussed below), though in any case it tracks linearly
94 for a given individual and scales across a population. In some animal models, notably in-vitro brain slices
95 [13], the electric field intensity can be tightly controlled allowing direct testing of electric field dose-
96 response.

97 Modeling studies predict that for low intensity range of applied current (i.e. 2 mA), induced electric
98 field in the brain is less than 1 V/m (Figure 1) [14]. These predictions have been directly [15-18] and
99 indirectly validated [19, 20]. Because of these low electric fields, it has been suggested that the primary
100 effects of tDCS are due to changes in the membrane potentials of neurons with most attention paid to
101 pyramidal grey matter neurons orientated orthogonal to the brain surface [13, 21] or to synaptic terminals
102 [22]. In this view, any effects of tDCS are secondary to changes in this polarization [23, 24]. Even when
103 other cell types may be implicated (e.g. glia, [25], the primary mechanism of tDCS is speculated to act
104 through polarization of these cell membranes [26].

105 Basic theory of tDCS suggests that membrane polarization would be polarity-specific and linear
106 with applied current intensity (i.e. generated electric field (EF)). This is because tDCS is low intensity (few
107 mA) and so considered to depend on subthreshold resting membrane potential changes rather than directly
108 inducing neuronal firing (e.g., 700-1000 mA used in ECT). Thus, assuming membrane polarization is the
109 key determinant for the effect of tDCS, it is reasonable to assume that increasing tDCS intensity will
110 increase effects size in general (Figure 1). However, this may strictly only apply in well-controlled
111 preparations; in the brain, responses may be non-linear and occur in a complex (e.g. non-linear,
112 homeostatic) manner. Therefore, a critical unanswered question is whether increasing current in the tDCS
113 range applied in humans (4mA or less) enhances neuromodulation and outcomes in a linear, or at least
114 monotonic manner. This question of linear dose response for a given polarity can be distinct from whether

115 there are any polarity specific effects. Notably, if one considers folding of the cortex and diffuse current
116 flow, tDCS produces mixed polarity effects under each stimulation electrode [22, 27]. This again
117 emphasizes that extrapolation from well-controlled animal studies can be fraught with oversimplification.

118 **Indications about intensity-response of tDCS from animal models**

119 Quiescent neurons are those that are not spontaneously firing action potentials (which is an
120 anomalous state because neurons in vivo are active); such neurons can be observed in brain slices with
121 normal superfusate. Application of electric fields to such quiescent neurons suggest a linear correlation
122 between induced membrane polarization and electric field intensity polarity (Figure 1) (i.e. the more
123 external electric field, the more neuronal polarization). However, this relationship has been thoroughly
124 tested only for intensities above those applicable to studies in humans (>10 V/m). For example, Bikson et
125 al. (2004) evaluated the effect of uniform DC electric field on neuronal excitability in a rat hippocampal
126 slices using electric field between 10 to 100 V/m [13]. These authors reported membrane polarization was
127 generally linear except when field intensities exceeded 80 V/m (equivalent to tens of mA for tDCS, which
128 resulted in non-linear firing, [13]. While it is reasonable to assume this linear relationship continues with
129 electric fields under 1 V/m (Figure 1), this awaits empirical evidence. Other studies have reported a linear
130 sensitivity of neurons to polarization with DC or low-frequency alternating current (AC), electric fields
131 ranging from 2 -15 V/m DC [21, 28] to 1-15 V/m AC [28-30]. We are not aware of any neurophysiological
132 response directly demonstrating linear polarization effects with tDCS relevant fields intensities (<1 V/m).
133 Theoretical neuron polarization models based on traditional electrical stimulation theory predict a linear
134 polarization across all sub-threshold intensities in quiescent neurons including tDCS ranges of < 1 V/m
135 [31].

136 Membrane polarization is easiest to measure in quiescent neurons. However, neurons in vivo are
137 active, not quiescent. Any dose response assessment should therefore be conducted in firing (non-quiescent)
138 neurons. Assessing dose-response relationships is more complex in this case because: 1) the properties of
139 the neuronal membrane changes with ongoing activity [31, 32]; and 2) any targeted neuron is coupled with

140 a larger population or entire network and its activity is presumably mediated by changes in network activity
141 [28].

142 Animal studies have demonstrated changes in network activity (0.2 V/m, [28]; 0.5 V/m [30] and
143 meta-plasticity (0.75 V/m, [33]) for electric fields <1 V/m but have not systematically evaluated a dose-
144 response within this range. We emphasize that showing an effect at one DCS intensity compared to no-
145 stimulation does not establish a (linear) dose response. Another complication is that “classical” animal
146 studies have applied electrodes on the surface of the brain with electric fields orders of magnitude above
147 those generated by tDCS in humans [34, 35]. Typically, these studies have used unit firing rate to measure
148 response; here again caution is warranted in assuming any dose response at high DCS intensity applied to
149 ranges below 1 V/m and in drawing direct comparison with measures obtained in humans, such as motor-
150 evoked potentials (MEPs).

151 These considerations aside, animal studies, using both low and high-intensity DCS, have shown
152 that the effects of DCS are activity (state) dependent, which indicates that the effects of any given DCS
153 dose may vary depending on the outcome measure (experiment). For example, Bikson and colleagues
154 (2013) showed that the direction of DCS modulation on synaptic efficacy depends on the afferent pathways;
155 indeed, in the same columns (small network) one pathway may be enhanced even as another is inhibited
156 [13, 22]. Frohlich et al. [21] and Reato et. al [28] have shown that the variation of DCS effects can depend
157 entirely on ongoing brain activity – evidently if tDCS modulates ongoing brain activity then the effect of
158 tDCS entirely depends on what endogenous activity is present. Fritch et al. [33] and Kornberg et al. [36]
159 showed pathway and activity state-dependent plasticity modulation by DCS. Although these findings do
160 not in themselves indicate that the dose-response of any given activity is not monotonic, they show that the
161 response to a given dose can categorically vary on different outcome measures (e.g. brain states). While,
162 on the one hand, the ongoing activity in brain slices (“brain state”) is abstracted from the in vivo case, on
163 the other hand, brain slices provide exquisite control and monitoring of brain state, supporting the testing
164 of hypothesis on the role of brain state in DCS intensity dose response.

165 In summary, in both quiescent and active neurons of animal brains there is (remarkably) no
166 comprehensive evidence for a linear dose-response relationship at electric field intensities below 1 V/m.
167 There is, however, evidence of neurophysiological changes at specific low intensities supporting that tDCS
168 can modulate brain function. Some dose response is expected in animal models (starting with no response
169 for a no-stimulation condition of 0 V/m) but the absence of clear escalation in response with intensities up
170 to 1 V/m (e.g. including 0.25 V/m, 0.5 V/m, 0.75 V/m, 1 V/m) is noteworthy and a critical area for future
171 studies.

172 We note that evidence for dose response from other neuromodulation approaches using supra-
173 threshold (high intensity) pulse approaches such as deep brain stimulation (DBS) [37, 38], TMS [39] and
174 transcranial electrical stimulation (TES) [19], do not establish a dose response for tDCS, which is sub-
175 threshold. Within those supra-threshold techniques, more intensity simply results in a high-likelihood
176 and/or number of recruited neurons. Evidence from low-intensity, sub-threshold, alternate waveforms such
177 as transcranial alternate current stimulation (tACS) or transcranial random noise stimulation (tRNS) can
178 also show non-linearity in dose-response as measured by TMS-MEP [40]. However, such data do not
179 provide direct evidence in support of non-linear tDCS dose-response given the presumed unique mechanism
180 of action when using a DC waveform. Finally, to foreshadow the following section, animal studies are
181 anatomically constrained, and generally record from a very small section of cortex. Results from such
182 preparation may not easily transfer to applications in humans, which lead to a much larger extent of
183 stimulated cortex and thus are influenced by the complex interactions with the convoluted cortical structure.

184 **Diffuse current flow in tDCS vs. HD-tDCS**

185 Prior to expanding on dose-response data in humans, some comments on the relationship between
186 applied current and resulting brain current flow patterns are critical. While dose of tDCS is defined by
187 operator controlled factors including current intensity [10], the electric field generated in the brain will vary
188 by individual and will fluctuate in space across the brain (Figure 2). Intra-cranial recording [15, 17],
189 imaging [41], and current flow models [2] show that traditional pad-based tDCS montages deliver current
190 flow across large brain areas including not just under, but in the brain regions between the electrodes (Figure

191 2, A and B). Many conventional tDCS montages can produce significant current flow through 30-70% of
192 the brain including deep brain structures [42]. Moreover, peak current is often seen between, rather than
193 under the electrodes [43]. The intensity and pattern of diffuse current flow and where peaks are generated
194 reflect idiosyncratic anatomical differences and so there is variation across individuals (Figure 2, Head #1
195 (A.1, B.1, C.1), Head #2 (A.2, B.2, C.2)) that is distinct from standard averaged head simulations (Figure
196 2, Head #3 (A.3, B.3, C.3)) [44, 45]. Attempts to develop a dose-response based on applied tDCS current
197 (typically fixed across subjects) should be interpreted in this context. For example, the conventional “M1-
198 SO” tDCS montage, used to probe the dose-response of M1 (see human neurophysiology below), is
199 predicted to produce as high electric fields in many regions afferent to M1 [42] (Figure 2,A). Therefore, the
200 intensity-response may depend on how each area of the network responds to increased current density and
201 then how the different brain areas interact. As we discuss later, one approach to account for this complexity
202 is to use multiple tDCS montages along with models of current flow to regress dose-response in human
203 studies.

204 Since the spatial distribution of stimulation could impact dose response, a complimentary approach
205 to conventional tDCS is the use of smaller HD electrodes. HD-tDCS electrode arrangements include
206 concentric ring configurations (e.g. 4x1 HD-tDCS; [46]) which applied to the (motor) cortex produce more
207 focal stimulation delivery (Figure 2, C). This might reduce variability in targeting across subjects [19]
208 compared to pad-based tDCS (Figure 2, A and B). HD montages can be designed to spare deep brain regions
209 or maximize current to deep structures [47]. With the goal of understanding current intensity dose-response
210 by stimulating a relatively smaller and more controlled area of cortex, concentric-ring HD-tDCS is
211 especially a useful tool in addition to pad-based tDCS. However, direct comparisons are few [48-50].

212 **Indications about intensity-response of tDCS from human neurophysiology**

213 In exploring dose response in humans, tDCS studies have relied heavily on MEP changes in
214 response to TMS to establish neurophysiological changes in motor regions by tDCS [4, 51]. In the most
215 basic experiments, the TMS-MEP threshold or MEP response to a fixed TMS intensity is measured before,

216 during and/or after application of tDCS. A linear dose response would predict that increasing intensity (i.e.,
217 > mA) would proportionally increase the degree of modulation (i.e., > TMS-MEP). Indeed, early canonical
218 studies in healthy subjects used a low-dose range (up to 1 mA for several minutes) and initially suggested
219 a monotonic relationship between tDCS intensity and TMS-MEP size.

220 While several subsequent studies replicated the basic findings at 1 mA [52], a more complex dose
221 response has emerged. Increasing stimulation intensity, increasing duration (in cases by >10 minutes),
222 and/or concurrent brain activation or pharmacological manipulation [53-58] can also change the extent and
223 direction of excitability changes measured by TMS-MEP and, so, the dose-response [59]. For example,
224 priming the motor region during “anodal” tDCS (asking subjects to activate hand muscles) can invert the
225 direction of TMS-MEP modulation suggesting that the direction is state dependent. Increasing “cathodal”
226 tDCS intensity to 2 mA can result in TMS-MEP enhancement [53]. Children also exhibited non-monotonic
227 dose-response but over a different intensity range. Indeed, as compared to adults [54] “cathodal”
228 stimulation became excitatory at only 1 mA. This difference in dose-response within children compared to
229 adults was consistent with altered brain electric field for small head sizes [60, 61].

230 As noted above, most of the extant clinical neurophysiology research has used conventional pad
231 tDCS, where current may be delivered to diverse brain regions (Figure 2, A and B) [15, 17]. To the extent
232 that any given measured response is influenced by current from more than one region (e.g. TMS- MEP is
233 influenced by current not only from the motor area but also from premotor regions and afferent deep brain
234 structures), then dose response will be related to how increasing current to each of these regions in aggregate
235 influences TMS response. Therefore, an important question is if using HD-tDCS, where more nuanced
236 control of current flow is predicted, is useful in dissecting and clarifying dose response [62, 63].

237 In summary, neurophysiological findings in humans indicate that tDCS outcomes are not
238 necessarily linear, nor even monotonic, with increasing tDCS intensity (even in the limited range of 1-2
239 mA). Moreover, the nature of modulation is profoundly influenced by variations in brain state. TMS-MEP
240 as a probe of brain function, represents a combination of complex measures itself influenced by several

241 physiological factors including the excitability of neuronal circuits at both cortical and spinal level [3] and
242 do not simply map to behavioral changes. In addition, TMS-MEP is typically measured after tDCS (i.e.,
243 offline) and thus may not always reflect the response to concurrent tDCS (i.e., online) effects, which
244 presumably accumulate during the stimulation period (as reinforced by data on tDCS duration) [4, 64].
245 Moreover, it is unclear whether non-motor cortex responds in a comparable manner following tDCS, which
246 has profound implications for cognitive neuroscience and neuro-rehabilitative efforts. More generally, the
247 notion that tDCS adjusts brain excitability and functions like a “sliding scale” (that is simply “measured”
248 by TMS) is an oversimplification [65, 66]. Rather, tDCS-induced excitability and plasticity changes may
249 reflect a mixture of complex changes in a number of different sets of excitatory and inhibitory synapses
250 [28, 67]; a possibility supported by recent TMS-MEP work that provides some evidence in humans against
251 a simple monotonic dose-response [53, 59]. As recently pointed out by Bestmann and Ward (2017) [11],
252 there is currently no data on the dose-response of tDCS that accounts for the current effectively delivered
253 to the brain, recent computational neural network modelling studies aside [68]. This is an obvious caveat
254 when interpreting the extant literature on non-linear effects of tDCS.

255

256 **Indications about dose-response from imaging studies**

257 PET, fMRI, and EEG studies in healthy populations corroborate the results from current flow
258 models that tDCS has distributed effects [69-72]. For example, Clemens et al. (2014), applied tDCS over
259 the right angular gyrus (AG) and induced large-scale changes in different resting state networks with
260 significant changes at the ventral lateral thalamic nucleus despite the region not being nominally targeted.
261 Hampstead and colleagues (2014) demonstrated polarity dependent BOLD signal change during task
262 performance [73] and resting-state connectivity [74] in healthy young participants such that these measures
263 were generally relatively enhanced with anodal stimulation but suppressed with cathodal stimulation.
264 Arterial Spin Labeling (ASL), considered a direct measure of blood flow, suggests a monotonic correlation
265 between tDCS dose (i.e., 0.8-2 mA) and regional cerebral blood flow underneath the anode [75]. Using

266 changes in fMRI signal as an index of cortical recovery in a patient who received successful visual
267 rehabilitation, Halko et al. (2011) reported correlations between the modeled electrical field and increased
268 task-related fMRI activation in areas under the anode as well as in perilesional visual areas [76]. Broadly,
269 these findings of a distributed effect of tDCS are not surprising when considering the diffuse current flow
270 with conventional tDCS application (Figure 2, A and B). But currently there is scant evidence for the dose-
271 response relationship of tDCS from neuroimaging. Future efforts should leverage different neuroimaging
272 measures of distributed activity change to tDCS. However, we note that in some cases the transfer function
273 between changes produced neural activity may itself not map linearly (Figure 1) onto the measures obtained
274 with neuroimaging [77-80], and tDCS may itself produce direct (e.g. changes in hemodynamics; [75, 81,
275 82] and indirect (artifact; [20]) signal changes in imaging data.

276

277 **Indications about dose-response from cognitive/behavioral outcomes in healthy population**

278 A narrow range of intensities were tested in tDCS cognitive and behavioral studies (95% of trials
279 used 1 or 2 mA) [83, 84] with few exceptions [5]. However, even within this small range, there are limited
280 data directly correlating effect size in tDCS human trials with current intensity [53]. For instance, the
281 influence of current intensity (i.e. 1 mA, 2 mA) was investigated on a working memory task among healthy
282 controls, indicating a non-monotonic current intensity dose-response [85]. In another study, none of the
283 examined intensities (i.e. 1mA, 2 mA) produced significant effects in a working memory task [86]. Cuypers
284 and colleagues (2013) indicated a dose-response relationship in a motor learning task with significant
285 enhancement in motor performance at 1.5 mA but not 1 mA [56]. We note the important statistical caveat
286 that a significant response at one dose, but not another, does not itself establish a difference *between* two
287 doses.

288 Most behavioral and cognitive studies have used large pad-sponge electrodes. Thus, any given
289 response is influenced by stimulation of more than one cortical region, and dose-response is reflecting the
290 amalgamation of current flow across many regions with varied intensity in brain areas (see below; Figure

291 3). The use of HD-tDCS would significantly reduce current spread, but given current spread even under
292 optimized HD-tDCS is greater than one gyri which is the size of a typical ROI. Use of HD-tDCS reduces
293 but not remove this confound.

294

295 **Indications about dose-response from functional outcomes in medically ill populations**

296 While tDCS is widely investigated as potential therapeutic tool to enhance cognitive rehabilitation in
297 neuropsychiatric disorders [87, 88], only a few studies explored dose-response and with a limited number
298 and range of dose. Protocol variations limit generalization across studies (e.g. electrode montages, cognitive
299 tasks, population inclusion criteria and type of disorder) on the role of intensity and there is a general
300 consensus that other factors such as the number of tDCS sessions broadly enhance efficacy [89-91]. In a
301 meta-analysis of tDCS trials for major depression, Brunoni et al. (2016) could not determine if current
302 intensity (mA) was positively associated with tDCS efficacy [92]. However, within a crossover design trial,
303 tinnitus relief was positively correlated with HD-tDCS current intensity [93]. Murry and colleges (2015)
304 investigated tDCS current intensity in chronic spinal cord injury patient in a single blind, sham controlled,
305 crossover study [94]; 2 mA ,but not 1 mA, significantly enhanced TMS-MEP modulation. Boggio and
306 colleagues explored effect of tDCS stimulation site (i.e. over DLPFC, over motor cortex) and intensity (i.e.
307 1 mA, 2 mA) in Parkinson's disease [95]. Results indicated an intensity and montage-specific effect with
308 only 2 mA anodal stimulation over DLPFC significantly improving accuracy of a working memory task.
309 Optimization of stimulation parameters (i.e. current intensity [0.1-0.4 mA], duration [5-20 min] with
310 respective steps of 0.1 mA and 5 min) for treatment of Parkinson's disease in primates indicated that total
311 charge (\sum current intensity \times duration of stimulation) is correlated with treatment outcome instead of current
312 intensity or stimulation duration [96]. In a case report, increasing current intensity (i.e. 1 mA to 3 mA)
313 enhanced and accelerated benefits in a schizophrenia patient [97]. In another study, feasibility of tDCS for
314 enhancing cognitive performance in schizophrenia using higher current intensity (i.e. 2 mA vs 1 mA) was
315 shown [98]. We emphasize that demonstrating efficacy of increased current intensity compared to non-
316 significant effect in commonly used tDCS current intensity (e.g. 1 mA) do not stablish current intensity

317 dose response. Investigation of dose response in patients require systematic escalation of current intensity
318 (see below; Figure 3), and would further benefits from an expanded current range - provided tolerability is
319 controlled [99].

320

321 **Use of current flow models to inform imaging, neurophysiological and behavioral studies of dose** 322 **response**

323 As noted above, intra-cranial measurements [15, 17], imaging [41], and models of current flow
324 show that conventional tDCS with large electrodes are placed “over” the target areas. In fact, they deliver
325 current to brain regions between the anode and the cathode (Figure 2, A and B) [2, 55]. This diffusivity and
326 lack of clear targeting complicates the analysis of response intensity and, at the same time, it reinforces that
327 computational models are needed to comprehensively investigate dose response. Using current flow
328 modeling, there have been: 1) Retrospective attempts to correlate electric field intensity in regions of
329 interest (ROI) with clinical outcomes using different montages (with fixed current), under the hypothesis
330 that montages that enhance electric fields in ROIs (for a given current) will enhance outcomes; 2)
331 Retrospective correlations of electric field intensity in ROIs with behavioral outcomes with a fixed montage
332 and fixed current considering how individual head anatomy differences affect brain current intensity, and
333 3) Prospective attempts to optimize the tDCS montage to deliver electric fields to ROIs, in some cases
334 accounting for individual anatomy, under the hypothesis that this would enhance outcomes compared to a
335 uniform tDCS montage [100].

336 Using current flow modeling, retrospective efforts comparing montages have provided indirect
337 evidence that electric field intensity produced by tDCS in a ROI correlates with enhanced clinical (e.g. pain,
338 [101] or neurophysiological outcomes (e.g. TMS MEP, [102]). Kim et al. (2014) investigated the
339 relationship between the behavioral outcomes in a verbal working memory task (WM) and variations in
340 electric field intensity over the dorsolateral prefrontal cortex (DLPFC) based on subject specific anatomy.
341 Participants who showed significant enhanced WM task performance (good responders) had significantly
342 higher electric field intensity over the DLPFC than other participants (bad responders), suggesting that

343 variability in behavioral outcomes of tDCS might be partly due to individual anatomical differences,
344 consistent with a monotonic dose response.

345 In some cases, current flow models have been used to optimize response to tDCS, but in these cases
346 an implicit assumption has been made about a local (tissue level) monotonic dose response, namely that
347 designing approaches that deliver more electric field to a given brain region will increase effect size. Several
348 attempts to individualize tDCS by using current flow models to optimize electric field to a target brain
349 region have centered around stroke patients where individual lesions produce unique distortion of brain
350 current flow patterns [103]. With the goal of optimizing the tDCS montage to maximize electric fields in
351 specific anatomical regions implicated in neurorehabilitation (e.g. identified by fMRI), approaches to
352 individualize HD-tDCS therapy were developed [28, 47] but, even if these trials were conducted, the
353 underlying assumption on dose response remains to be validated. Several studies have used current flow
354 modeling to design an optimized HD-tDCS montage (across subjects) for specific ROIs. In applications
355 including pain control [104], tinnitus [93], motion perception [105], verbal learning and memory function
356 [63], such HD approaches have yielded encouraging effect sizes, often larger than those using conventional
357 tDCS montages. However, these HD-tDCS montages typically reduce the spatial extent of current in the
358 brain rather than electric field intensity [47] and reinforce the role of the spatial distribution of current flow
359 in influencing dose response rather than providing support for a dose-response itself.

360 **Methodology to systematically investigate dose-response**

361 The thesis of this paper - that there is deficiency in the current knowledge on tDCS intensity dose
362 response - in turn indicates a need for expanded and more rigorous current intensity dose response testing
363 [106]. Approaches to experimental design of dose-response studies are discussed in this section (Figure 3),
364 two in animal (in-vitro and in-vivo) and four in human trials (fixed current with conventional pad electrodes,
365 controlled electric field with conventional pad electrodes, fixed current with high-definition electrodes, and
366 controlled electric field with high definition electrodes).

367 Animal studies provide special opportunities to explore dose-response relationships, but only if
368 conducted in meaningful ways to the human stimulation [26]. In-vitro brain slice experiment uses an

369 escalation of electric field intensity (Figure 3 A.1), which is more meaningful to control than applied
370 current. Using specific stimulation techniques (i.e. large parallel wires;[13]), with a uniform electric field
371 the entire tissue is exposed to a single magnitude and electric field direction (e.g. 1 V/m normal to the
372 cortical surface). An experimental measure from brain slices, which can be electrophysiological or
373 molecular, can then be related to the applied electric field as a proxy for local tissue response to escalating
374 electric field intensity. While some variability in response to a given electric field is expected in any
375 experimental system, brain slices offer the possibility for high-throughput experimentation yielding results
376 with high confidence.

377 In-vivo experiments involve non-invasive stimulation, under current control [26]. The animal
378 anatomy will determine the resulting electric field in the ROI, and varied electric field across other brain
379 regions which may influence outcomes (Figure 3 A.2). Brain electric field distribution can be predicted
380 using current flow models [5, 107, 108]. For any given applied current, significant inter-species variation
381 and some inter-animal variation is expected in the resulting brain electric field. An experimental measure
382 from animals, which can span electrophysiological, molecular, or behavioral, is correlated with the applied
383 current. Variability in response across animals for a given dose, can be minimized through experimental
384 design.

385 In a conventional tDCS current intensity dose response experiments, two or more stimulation
386 currents (e.g. 1 mA and 2 mA) are applied across individuals using conventional sponge-pad electrodes
387 (Figure B.2). While straightforward from a design perspective, this approach has several methodological
388 caveats. Applying fixed current in a population lead to significant inter-individual differences in brain EF
389 that are a function of each subject's head anatomy [11]. Considering a relatively wide distribution of brain
390 EF in ROI, means that some subjects in the "low dose" (e.g. 1 mA) group may have a higher EF in the ROI
391 than some subjects in the "high dose" (e.g. 2 mA) group. The range of doses typically explored (e.g. 2x
392 from 1 mA to 2 mA) is less than the range of sensitivity across subjects (e.g. 3-5x across healthy adults
393 [44]). Use of a wider current range (if tolerated) mediates these overlaps, but does not mitigate the large
394 variance in effective brain current with this approach.

395 Still more problematic is that with conventional tDCS montages, electric field is generated across
396 wide regions of the brain, with the location of peak electric field varying across individuals, and often not
397 occurring “under” the electrodes [2]. These issues compound such that the average electric field in a none
398 ROI at the “low dose” can be higher than the electric field in the nominal ROI under high-dose. Ultimately,
399 using this simplistic current intensity dose-response experimental design (Figure 3 B.2), one must interpret
400 the effects of tDCS, and so the dose response, as reflecting the amalgamation of current flow across many
401 regions with varied intensity.

402 The above concerns can only be partially mitigated by normalizing electric field intensity to the
403 ROI for each subject (Figure 3 B.1). In a second experimental design for human trials, using individual
404 MRI and modeling the individualized current needed for each subject is determined to produce a consistent
405 electric field in a given ROI. Notably in this method each subject will receive a unique current for a given
406 target electric field (e.g. 0.5 V/m) in the ROI, and this current may vary several-fold variation in current
407 applied across individuals (e.g. 0.6 mA, 1.4 mA, 2.1 mA...) as a result of the aforementioned inter-
408 individual anatomical differences [44]. Dose escalation therefore involved increased electric field in the
409 ROI (e.g. 0.5 V/m, 1 V/m) not applying a multiple to the individual applied current for each subject. An
410 experimental measure from the trial, which can span electrophysiological, imaging, or behavioral, is
411 correlated with the electric field in the ROI. Because conventional tDCS pads are still used, current can
412 flow through the brain with maximum electric field not necessarily in the ROI and not in a consistent
413 location across subjects [44]. To the extent that current flow to other brain regions influences the outcome
414 measure, it is a problem that the electric field intensity is not controlled outside the ROI.

415 An addition to the fixed-current approach (Figure 3 B.2) is to retrospectively model individual
416 current flow and then correlate with experimental measure with the post-hoc calculated electric field in the
417 nominal ROI. This leads to a distribution of predicted electric fields with some subjects in the “low dose”
418 current group (e.g. 1 mA) presenting a higher electric field in the ROI than some subjects in the “high dose”
419 current group (e.g. 2 mA). This post-hoc modeling may not meaningfully mediate the concern with broad
420 and varied brain current flow across subjects using pad montages, as the relative electric field distribution

421 across individuals will vary.

422 Using High-Definition tDCS, and specifically the 4x1 montage, current is restricted to defined brain
423 regions (ROI within the electrode ring); the peak electric field is within this brain region and thus consistent
424 across subjects. In a third experimental design for human trials, a dose response trial design using 4x1 HD-
425 tDCS and the fixed current escalation method (e.g. 1 mA, 2 mA) provides evidence at the *population* level
426 if increased intensity at the ROI is correlated with an outcome measure (Figure 3 C.2). Focal EF produced
427 by HD montage provide a substrate for controlling impact of stimulating functional/structural connected
428 areas outside the ROI (Figure 3, C). Thus, an essential difference from conventional pad-tDCS is that
429 electric fields outside the ROI are low enough that increasing applied current still does not result in
430 significant current outside the ROI.

431 In a fourth experimental design for human trials, using the 4x1 High-Definition tDCS montage,
432 individualized modeling based in subject-specific MRI can be used to normalize the electric field across
433 individuals (Figure 3 C.1). An experimental measure from the trial, which can span electrophysiological,
434 imaging, or behavioral, can be meaningfully correlated with the electric field in the ROI. It is possible
435 using the fixed current 4x1 High-Definition tDCS (Figure 3 C.2) to use individual MRIs for post-hoc
436 modeling of electric fields in the ROI, which in contrast to the fixed electric field approach leads a
437 distribution of electric field values. This scattered representation of electric fields in the ROI is not
438 deleterious to dose-response analysis and in fact may lead to a wider variation and range of electric fields
439 in the ROI.

440 In all four experimental noted designs for human trial, variability in response for a given dose (fixed
441 current or electric field controlled) is expected reflecting individual neurophysiological and brain state
442 differences, which may be mitigate through rigorous experimental design (e.g. subject inclusion criteria,
443 testing environment) but never eliminated. These physiological variations are compounded by any
444 limitations in dose-response design described above which further emphasizes the need for careful
445 consideration of dose-response experimental design. The four classifications described above by no means
446 fully characterizes the diversity of approaches and issues which must be considered for meaningful tDCS

447 dose-response experiments [106, 109-112] and includes fundamental rigor in tDCS methodology [113]. For
448 example, neural network modelling approaches can help generating hypotheses about the non-linear
449 dynamics in neural activity under escalating tDCS dose [68].

450 **Synopsis**

451 Despite ongoing advances in the science of tDCS, we currently do not have a clear understanding
452 of dose-response relationships in tDCS and principal open questions to be answered (Table 1). This limits
453 empirical choice about the most efficacious stimulation protocol in a given context, renders inter-individual
454 (and hence between study) comparison prone to complication, and hampers non-spurious assessment about
455 the sources of tDCS response variability [114].

456 The biophysics of tDCS, namely the fact that increasing current produces a linear increase in brain
457 electric field (Figure 1) [9] and, then, presumably membrane polarization [13], is only a starting point and
458 it does not allow conclusions that increasing tDCS intensity enhances a given neurophysiological,
459 behavioral, or clinical outcome. A simplistic hypothesis on dose response emerged from classical animal
460 studies (circa 1960) – anode/cathode increases/decreases excitability and plasticity - but modern efforts
461 suggest a more nuanced dose-response. Investigations in animal studies provide a rich substrate for DCS
462 mechanisms but are surprisingly lacking in electric fields relevant for humans (i.e. testing multiple
463 intensities below 1 V/m). Studies using TMS-evoked potentials have also provided an extensive substrate
464 to design and understand tDCS protocols [59], but challenges simple notions of linear dose-response of
465 tDCS in humans on a group or individual level [52, 53].

466 Canonical neurophysiological studies tested intensities only up to 1 mA in the absence of tasks [4,
467 24] and suggested a simple polarity response consistent with classical animal studies. However,
468 increasingly higher intensities are adopted (2 or 1.5 mA; [95, 115, 116] and tDCS is typically used in
469 combination with training [117], where evidence suggest a multi-factorial dose response that is not
470 necessarily monotonic with current intensity nor does it follow a simple excitability-change rule
471 (anode/cathode, boost/suppress). Imaging studies support a complex response across brain regions.
472 Computational models are a tool to normalize brain current intensity across individuals but are themselves

473 subject to assumptions about local dose response (e.g. doubling local current intensity in a ROI increases
474 its response) to current that remains to be validated.

475 In conclusion, extant data on tDCS mechanisms are inconclusive in regards to whether or not
476 graded changes in applied current, and hence brain electric fields, enhance effect sizes in a linear or
477 monotonic way. Put simply, we still do not know whether more intensity of electric field in a given brain
478 area supports greater neurophysiological or behavioral outcomes [114]. We believe that this is a crucial
479 point given extensive ongoing research on tDCS. Noting the heterogeneity of the literature on tDCS dose-
480 response [118], we urgently need to understand how much current we should deliver and how different
481 brain regions will respond. We suggest rigorous efforts to quantify dose-response in humans, regardless of
482 approach and outcome measure, will benefit from including computational current flow models. Despite
483 these conclusions, we emphasize that uncertainty about dose-response does not necessarily diminish the
484 impact of exhaustive testing of tDCS effects, its potential utility, or the value of an extensive mechanistic
485 analysis that already exists on tDCS.

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496 **References:**

- 497 [1] Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research
498 with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul*
499 2012;5(3):175-95.
- 500 [2] Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial
501 direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular
502 pad. *Brain Stimul* 2009;2(4):201-7. e1.
- 503 [3] Iyer M, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann E. Safety and cognitive effect of
504 frontal DC brain polarization in healthy individuals. *Neurology* 2005;64(5):872-5.
- 505 [4] Nitsche M, Paulus W. Excitability changes induced in the human motor cortex by weak
506 transcranial direct current stimulation. *J Physiol* 2000;527(3):633-9.
- 507 [5] Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial
508 direct current stimulation: evidence based update 2016. *Brain Stimul* 2016;9(5):641-61.
- 509 [6] Marshall L, Mölle M, Siebner HR, Born J. Bifrontal transcranial direct current stimulation slows
510 reaction time in a working memory task. *BMC Neurosci* 2005;6(1):1.
- 511 [7] Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, et al. Noninvasive cortical
512 stimulation with transcranial direct current stimulation in Parkinson's disease. *Mov Disord*
513 2006;21(10):1693-702.
- 514 [8] Liebetanz D, Klinker F, Hering D, Koch R, Nitsche MA, Pöschka H, et al. Anticonvulsant
515 Effects of Transcranial Direct-current Stimulation (tDCS) in the Rat Cortical Ramp Model of Focal
516 Epilepsy. *Epilepsia* 2006;47(7):1216-24.
- 517 [9] Bikson M, Truong DQ, Mourdoukoutas AP, Aboseria M, Khadka N, Adair D, et al. Modeling
518 sequence and quasi-uniform assumption in computational neurostimulation. *Prog Brain Res* 2015;222:1-
519 23.
- 520 [10] Peterchev AV, Wagner TA, Miranda PC, Nitsche MA, Paulus W, Lisanby SH, et al.
521 Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting
522 practices. *Brain Stimul* 2012;5(4):435-53.
- 523 [11] Bestmann S, Ward N. Are current flow models for transcranial electrical stimulation fit for
524 purpose? *Brain Stimul* 2017.
- 525 [12] Bikson M, Rahman A, Datta A. Computational models of transcranial direct current stimulation.
526 *Clin EEG Neurosci* 2012;43(3):176-83.
- 527 [13] Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, et al. Effects of uniform
528 extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J Physiol*
529 2004;557(1):175-90.
- 530 [14] Truong DQ, Magerowski G, Blackburn GL, Bikson M, Alonso-Alonso M. Computational
531 modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose
532 guidelines. *Neuroimage Clin* 2013;2:759-66.
- 533 [15] Huang Y, Liu AA, Lafon B, Friedman D, Dayan M, Wang X, et al. Measurements and models of
534 electric fields in the in vivo human brain during transcranial electric stimulation. *Elife* 2017;6:e18834.
- 535 [16] Jog MV, Smith RX, Jann K, Dunn W, Lafon B, Truong D, et al. In-vivo Imaging of Magnetic
536 Fields Induced by Transcranial Direct Current Stimulation (tDCS) in Human Brain using MRI. *Sci Rep*
537 2016;6.
- 538 [17] Opitz A, Falchier A, Yan C-G, Yeagle EM, Linn GS, Megevand P, et al. Spatiotemporal structure
539 of intracranial electric fields induced by transcranial electric stimulation in humans and nonhuman
540 primates. *Sci Rep* 2016;6.
- 541 [18] Esmaeilpour Z, Milosevic M, Azevedo K, Khadka N, Navarro J, Brunoni A, et al. Proceedings#
542 21. Intracranial voltage recording during transcranial direct current stimulation (tDCS) in human subjects
543 with validation of a standard model. *Brain Stimul* 2017;10(4):e72-e5.

544 [19] Edwards D, Cortes M, Datta A, Minhas P, Wassermann EM, Bikson M. Physiological and
545 modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition
546 tDCS. *Neuroimage* 2013;74:266-75.

547 [20] Antal A, Bikson M, Datta A, Lafon B, Dechent P, Parra LC, et al. Imaging artifacts induced by
548 electrical stimulation during conventional fMRI of the brain. *Neuroimage* 2014;85:1040-7.

549 [2] Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity.
550 *Neuron* 2010;67(1):129-43.

551 [22] Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct
552 current stimulation: somatic and synaptic terminal effects. *J Physiol* 2013;591(10):2563-78.

553 [23] Sun Y, Lipton JO, Boyle LM, Madsen JR, Goldenberg MC, Pascual-Leone A, et al. Direct
554 current stimulation induces mGluR5-dependent neocortical plasticity. *Ann Neurol* 2016;80(2):233-46.

555 [24] Nitsche M, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological
556 modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J*
557 *Physiol* 2003;553(1):293-301.

558 [25] Monai H, Ohkura M, Tanaka M, Oe Y, Konno A, Hirai H, et al. Calcium imaging reveals glial
559 involvement in transcranial direct current stimulation-induced plasticity in mouse brain. *Nat Commun*
560 2016;7.

561 [26] Jackson MP, Rahman A, Lafon B, Kronberg G, Ling D, Parra LC, et al. Animal models of
562 transcranial direct current stimulation: Methods and mechanisms. *Clin Neurophysiol* 2016;127(11):3425-
563 54.

564 [27] Lafon B, Rahman A, Bikson M, Parra LC. Direct current stimulation alters neuronal input/output
565 function. *Brain Stimul* 2017;10(1):36-45.

566 [28] Reato D, Rahman A, Bikson M, Parra LC. Low-intensity electrical stimulation affects network
567 dynamics by modulating population rate and spike timing. *J Neurosci* 2010;30(45):15067-79.

568 [29] Chan C, Nicholson C. Modulation by applied electric fields of Purkinje and stellate cell activity
569 in the isolated turtle cerebellum. *J Physiol* 1986;371(1):89-114.

570 [30] Deans JK, Powell AD, Jefferys JG. Sensitivity of coherent oscillations in rat hippocampus to AC
571 electric fields. *J Physiol* 2007;583(2):555-65.

572 [31] Radman T, Ramos RL, Brumberg JC, Bikson M. Role of cortical cell type and morphology in
573 subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul* 2009;2(4):215-
574 28. e3.

575 [32] Paulus W, Rothwell JC. Membrane resistance and shunting inhibition: where biophysics meets
576 state-dependent human neurophysiology. *J Physiol* 2016.

577 [33] Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current
578 stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning.
579 *Neuron* 2010;66(2):198-204.

580 [34] Bindman LJ, Lippold O, Redfearn J. The action of brief polarizing currents on the cerebral cortex
581 of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *J Physiol*
582 1964;172(3):369.

583 [35] Gartside IB. Mechanisms of sustained increases of firing rate of neurones in the rat cerebral
584 cortex after polarization: role of protein synthesis. *Nature* 1968;220(5165):383-4.

585 [36] Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP
586 and LTD: activity dependence and dendritic effects. *Brain Stimul* 2017;10(1):51-8.

587 [37] Yamamoto T, Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C. Deep brain stimulation
588 for the treatment of parkinsonian, essential, and poststroke tremor: a suitable stimulation method and
589 changes in effective stimulation intensity. *J Neurosurg* 2004;101(2):201-9.

590 [38] Cif L, Ruge D, Gonzalez V, Limousin P, Vasques X, Hariz MI, et al. The influence of deep brain
591 stimulation intensity and duration on symptoms evolution in an OFF stimulation dystonia study. *Brain*
592 *Stimul* 2013;6(4):500-5.

593 [39] Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhael P, Ella R, et al. Repetitive transcranial
594 magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity.
595 *Neuropsychopharmacology* 2002;27(4):638-45.

596 [40] Moliadze V, Antal A, Paulus W. Close to threshold transcranial electrical stimulation
597 preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain*
598 *Stimul* 2012;5(4):505-11.

599 [41] Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, et al. How does transcranial DC
600 stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur J*
601 *Neurosci* 2005;22(2):495-504.

602 [42] DaSilva AF, Mendonca ME, Zaghi S, Lopes M, DosSantos MF, Spierings EL, et al. tDCS-
603 induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache*
604 2012;52(8):1283-95.

605 [43] Seibt O, Brunoni AR, Huang Y, Bikson M. The pursuit of DLPFC: non-neuronavigated methods
606 to target the left dorsolateral pre-frontal cortex with symmetric bicephalic transcranial direct current
607 stimulation (tDCS). *Brain Stimul* 2015;8(3):590-602.

608 [44] Datta A, Truong D, Minhas P, Parra LC, Bikson M. Inter-individual variation during transcranial
609 direct current stimulation and normalization of dose using MRI-derived computational models. *Front*
610 *Psychiatry* 2012.

611 [45] Huang Y, Parra LC, Haufe S. The New York Head—a precise standardized volume conductor
612 model for EEG source localization and tES targeting. *Neuroimage* 2016;140:150-62.

613 [46] Alam M, Truong DQ, Khadka N, Bikson M. Spatial and polarity precision of concentric high-
614 definition transcranial direct current stimulation (HD-tDCS). *Phys Med Biol* 2016;61(12):4506.

615 [47] Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC. Optimized multi-electrode stimulation
616 increases focality and intensity at target. *J Neural Eng* 2011;8(4):046011.

617 [48] Gbadeyan O, Steinhauser M, McMahon K, Meinzer M. Safety, tolerability, blinding efficacy and
618 behavioural effects of a novel MRI-compatible, high-definition tDCS set-up. *Brain Stimul* 2016;9(4):545-
619 52.

620 [49] Kuo H-I, Bikson M, Datta A, Minhas P, Paulus W, Kuo M-F, et al. Comparing cortical plasticity
621 induced by conventional and high-definition 4×1 ring tDCS: a neurophysiological study. *Brain Stimul*
622 2013;6(4):644-8.

623 [50] Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of prefrontal bipolar and high-definition
624 transcranial direct current stimulation on cortical reactivity and working memory in healthy adults.
625 *Neuroimage* 2017;152:142-57.

626 [51] Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor
627 cortex stimulation in humans. *Neurology* 2001;57(10):1899-901.

628 [52] Strube W, Bunse T, Nitsche MA, Nikolaeva A, Palm U, Padberg F, et al. Bidirectional variability
629 in motor cortex excitability modulation following 1 mA transcranial direct current stimulation in healthy
630 participants. *Physiol Rep* 2016;4(15):e12884.

631 [53] Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche M. Partially non-linear stimulation
632 intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J Physiol*
633 2013;591(7):1987-2000.

634 [54] Moliadze V, Schmanke T, Andreas S, Lyzhko E, Freitag CM, Siniatchkin M. Stimulation
635 intensities of transcranial direct current stimulation have to be adjusted in children and adolescents. *Clin*
636 *Neurophysiol* 2015;126(7):1392-9.

637 [55] Kidgell DJ, Daly RM, Young K, Lum J, Tooley G, Jaberzadeh S, et al. Different current
638 intensities of anodal transcranial direct current stimulation do not differentially modulate motor cortex
639 plasticity. *Neural Plast* 2013;2013.

640 [56] Cuypers K, Leenus DJ, van den Berg FE, Nitsche MA, Thijs H, Wenderoth N, et al. Is motor
641 learning mediated by tDCS intensity? *PLoS One* 2013;8(6):e67344.

642 [57] Ho K-A, Taylor JL, Chew T, Gálvez V, Alonzo A, Bai S, et al. The effect of transcranial direct
643 current stimulation (tDCS) electrode size and current intensity on motor cortical excitability: evidence
644 from single and repeated sessions. *Brain Stimul* 2016;9(1):1-7.

645 [58] Ammann C, Lindquist MA, Celnik PA. Response variability of different anodal transcranial
646 direct current stimulation intensities across multiple sessions. *Brain Stimul* 2017;10(4):757-763.

647 [59] Jamil A, Batsikadze G, Kuo HI, Labruna L, Hasan A, Paulus W, et al. Systematic evaluation of
648 the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current
649 stimulation. *J Physiol* 2017;595(4):1273-88.

650 [60] Minhas P, Bikson M, Woods AJ, Rosen AR, Kessler SK, editors. Transcranial direct current
651 stimulation in pediatric brain: a computational modeling study. *Conf Proc IEEE Eng Med Biol Soc* 2012;
652 2012: 859-62.

653 [61] Kessler SK, Minhas P, Woods AJ, Rosen A, Gorman C, Bikson M. Dosage considerations for
654 transcranial direct current stimulation in children: a computational modeling study. *PLoS One*
655 2013;8(9):e76112.

656 [62] Caparelli-Daquer EM, Zimmermann TJ, Mooshagian E, Parra LC, Rice JK, Datta A, et al.,
657 editors. A pilot study on effects of 4× 1 high-definition tDCS on motor cortex excitability. *Conf*
658 *Proc IEEE Eng Med Biol Soc* 2012; 2012: 735-8.

659 [63] Nikolin S, Loo CK, Bai S, Dokos S, Martin DM. Focalised stimulation using high definition
660 transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory
661 functioning. *Neuroimage* 2015;117:11-9.

662 [64] Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W. Level of action of
663 cathodal DC polarisation induced inhibition of the human motor cortex. *Clin Neurophysiol*
664 2003;114(4):600-4.

665 [65] Hämmerer D, Bonaiuto J, Klein-Flügge M, Bikson M, Bestmann S. Selective alteration of human
666 value decisions with medial frontal tDCS is predicted by changes in attractor dynamics. *Sci Rep*
667 2016;6:25160.

668 [66] Weiss M, Lavidor M. When less is more: evidence for a facilitative cathodal tDCS effect in
669 attentional abilities. *J Cogn Neurosci* 2012;24(9):1826-33.

670 [67] Rahman A, Lafon B, Parra LC, Bikson M. Direct current stimulation boosts synaptic gain and
671 cooperativity in vitro. *J Physiol* 2017;595(11):3535-3547.

672 [68] Bonaiuto JJ, Bestmann S. Understanding the nonlinear physiological and behavioral effects of
673 tDCS through computational neurostimulation. *Prog Brain Res* 2015;222:75-103.

674 [69] Meinzer M, Antonenko D, Lindenberg R, Hetzer S, Ulm L, Avirame K, et al. Electrical brain
675 stimulation improves cognitive performance by modulating functional connectivity and task-specific
676 activation. *J Neurosci* 2012;32(5):1859-66.

677 [70] Antal A, Polania R, Schmidt-Samoa C, Dechent P, Paulus W. Transcranial direct current
678 stimulation over the primary motor cortex during fMRI. *Neuroimage* 2011;55(2):590-6.

679 [71] Mangia AL, Pirini M, Cappello A. Transcranial direct current stimulation and power spectral
680 parameters: a tDCS/EEG co-registration study. *Front Hum Neurosci* 2014;8:601.

681 [72] Kunze T, Hunold A, Haueisen J, Jirsa V, Spiegler A. Transcranial direct current stimulation
682 changes resting state functional connectivity: A large-scale brain network modeling study. *Neuroimage*
683 2016;140:174-187.

684 [73] Hampstead BM, Brown GS, Hartley JF. Transcranial Direct Current Stimulation Modulates
685 Activation and Effective Connectivity During Spatial Navigation. *Brain Stimulation* 2014;7(2):314-24.

686 [74] Krishnamurthy V, Gopinath K, Brown GS, Hampstead BM. Resting-state fMRI reveals enhanced
687 functional connectivity in spatial navigation networks after transcranial direct current stimulation.
688 *Neurosci Lett* 2015;604:80-5.

689 [75] Zheng X, Alsop DC, Schlaug G. Effects of transcranial direct current stimulation (tDCS) on
690 human regional cerebral blood flow. *Neuroimage* 2011;58(1):26-33.

691 [76] Halko M, Datta A, Plow EB, Scaturro J, Bikson M, Merabet LB. Neuroplastic changes following
692 rehabilitative training correlate with regional electrical field induced with tDCS. *Neuroimage*
693 2011;57(3):885-91.

694 [77] Heeger DJ, Huk AC, Geisler WS, Albrecht DG. Spikes versus BOLD: what does neuroimaging
695 tell us about neuronal activity? *Nat Neurosci* 2000;3:631-2.

696 [78] Arthurs OJ, Boniface S. How well do we understand the neural origins of the fMRI BOLD
697 signal? *Trends Neurosci* 2002;25(1):27-31.

698 [79] Boussida S, Traoré AS, Durif F. Mapping of the brain hemodynamic responses to sensorimotor
699 stimulation in a rodent model: A BOLD fMRI study. *PLoS One* 2017;12(4):e0176512.

700 [80] Horwitz B. Relating fMRI and PET signals to neural activity by means of large-scale neural
701 models. *Neuroinformatics* 2004;2(2):251-66.

702 [81] Homan P, Kindler J, Federspiel A, Flury R, Hubl D, Hauf M, et al. Muting the voice: a case of
703 arterial spin labeling-monitored transcranial direct current stimulation treatment of auditory verbal
704 hallucinations. *Am J Psychiatry* 2011;168(8):853-4.

705 [82] Stagg CJ, Lin RL, Mezue M, Segerdahl A, Kong Y, Xie J, et al. Widespread modulation of
706 cerebral perfusion induced during and after transcranial direct current stimulation applied to the left
707 dorsolateral prefrontal cortex. *J Neurosci* 2013;33(28):11425-31.

708 [83] Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of Transcranial
709 Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimulation* 2016;10(5):983-985.

710 [84] Stephens JA, Jones KT, Berryhill ME. Task demands, tDCS intensity, and the COMT val 158
711 met polymorphism impact tDCS-linked working memory training gains. *Sci Rep* 2017;7(1):13463.

712 [85] Hoy KE, Emonson MR, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the
713 limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls.
714 *Neuropsychologia* 2013;51(9):1777-84.

715 [86] Teo F, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Investigating the role of current strength in tDCS
716 modulation of working memory performance in healthy controls. *Front Psychiatry* 2011;2:45.

717 [87] Cappon D, Jahanshahi M, Bisiacchi P. Value and efficacy of transcranial direct current
718 stimulation in the cognitive rehabilitation: a critical review since 2000. *Front Neurosci* 2016;10:157.

719 [88] Hampstead BM, Sathian K, Bikson M, Stringer AY. Combined mnemonic strategy training and
720 high-definition transcranial direct current stimulation for memory deficits in mild cognitive impairment.
721 *Alzheimers Dement (N Y)* 2017;3(3):459-470.

722 [89] Fiori V, Coccia M, Marinelli CV, Vecchi V, Bonifazi S, Ceravolo MG, et al. Transcranial direct
723 current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. *J Cogn Neurosci*
724 2011;23(9):2309-23.

725 [90] Jung I-Y, Lim JY, Kang EK, Sohn HM, Paik N-J. The factors associated with good responses to
726 speech therapy combined with transcranial direct current stimulation in post-stroke aphasic patients. *Ann*
727 *Rehabil Med* 2011;35(4):460-9.

728 [91] Marangolo P, Fiori V, Campana S, Calpagnano MA, Razzano C, Caltagirone C, et al. Something
729 to talk about: enhancement of linguistic cohesion through tDCS in chronic non fluent aphasia.
730 *Neuropsychologia* 2014;53:246-56.

731 [92] Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct
732 current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *BJPsych*
733 *Open* 2016;208(6):522-31.

734 [93] Shekhawat GS, Sundram F, Bikson M, Truong D, De Ridder D, Stinear CM, et al. Intensity,
735 duration, and location of high-definition transcranial direct current stimulation for tinnitus relief.
736 *Neurorehabil Neural Repair* 2016;30(4):349-59.

737 [94] Murray LM, Edwards DJ, Ruffini G, Labar D, Stampas A, Pascual-Leone A, et al. Intensity
738 dependent effects of transcranial direct current stimulation on corticospinal excitability in chronic spinal
739 cord injury. *Arch Phys Med Rehabil* 2015;96(4):S114-S21.

740 [95] Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, et al. Effects of
741 transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J Neurol*
742 *Sci* 2006;249(1):31-8.

743 [96] Li H, Lei X, Yan T, Li H, Huang B, Li L, et al. The temporary and accumulated effects of
744 transcranial direct current stimulation for the treatment of advanced Parkinson's disease monkeys. *Sci*
745 *Rep* 2015;5:12178.

746 [97] Andrade C. Once-to twice-daily, 3-year domiciliary maintenance transcranial direct current
747 stimulation for severe, disabling, clozapine-refractory continuous auditory hallucinations in
748 schizophrenia. *J ECT* 2013;29(3):239-42.

749 [98] Hoy KE, Arnold SL, Emonson MR, Daskalakis ZJ, Fitzgerald PB. An investigation into the
750 effects of tDCS dose on cognitive performance over time in patients with schizophrenia. *Schizophr Res*
751 2014;155(1):96-100.

752 [99] Nitsche MA, Bikson M. Extending the parameter range for tDCS: Safety and tolerability of 4 mA
753 stimulation. *Brain Stimul* 2017;10(3):541:542.

754 [100] Bikson M, Rahman A, Datta A, Fregni F, Merabet L. High-Resolution Modeling Assisted Design
755 of Customized and Individualized Transcranial Direct Current Stimulation Protocols. *Neuromodulation*
756 2012;15(4):306-15.

757 [101] Mendonca ME, Santana MB, Baptista AF, Datta A, Bikson M, Fregni F, et al. Transcranial DC
758 stimulation in fibromyalgia: optimized cortical target supported by high-resolution computational models.
759 *J Pain* 2011;12(5):610-7.

760 [102] Bikson M, Datta A, Rahman A, Scaturro J. Electrode montages for tDCS and weak transcranial
761 electrical stimulation: role of "return" electrode's position and size. *Clin Neurophysiol*
762 2010;121(12):1976.

763 [103] Datta A, Baker JM, Bikson M, Fridriksson J. Individualized model predicts brain current flow
764 during transcranial direct-current stimulation treatment in responsive stroke patient. *Brain Stimul*
765 2011;4(3):169-74.

766 [104] Castillo-Saavedra L, Gebodh N, Bikson M, Diaz-Cruz C, Brandao R, Coutinho L, et al. Clinically
767 effective treatment of fibromyalgia pain with high-definition transcranial direct current stimulation: Phase
768 II open-label dose optimization. *J Pain* 2016;17(1):14-26.

769 [105] Zito GA, Senti T, Cazzoli D, Müri RM, Mosimann UP, Nyffeler T, et al. Cathodal HD-tDCS on
770 the right V5 improves motion perception in humans. *Front Behav Neurosci* 2015;9.

771 [106] Giordano J, Bikson M, Kappenman ES, Clark VP, Coslett HB, Hamblin MR, et al. Mechanisms
772 and effects of transcranial direct current stimulation. *Dose-Response* 2017;15(1):1559325816685467.

773 [107] Jackson MP, Truong D, Brownlow ML, Wagner JA, McKinley RA, Bikson M, et al. Safety
774 parameter considerations of anodal transcranial Direct Current Stimulation in rats. *Brain Behav Immun*
775 2017;64:152-161.

776 [108] Márquez-Ruiz J, Leal-Campanario R, Sánchez-Campusano R, Molaee-Ardekani B, Wendling F,
777 Miranda PC, et al. Transcranial direct-current stimulation modulates synaptic mechanisms involved in
778 associative learning in behaving rabbits. *Proc Natl Acad Sci U S A* 2012;109(17):6710-5.

779 [109] Antal A, Alekseichuk I, Bikson M, Brockmüller J, Brunoni A, Chen R, et al. Low intensity
780 transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clin*
781 *Neurophysiol* 2017;128(9):1774-809.

782 [110] Sánchez-Kuhn A, Pérez-Fernández C, Cánovas R, Flores P, Sánchez-Santed F. Transcranial
783 direct current stimulation as a motor neurorehabilitation tool: an empirical review. *Biomed Eng Online*
784 2017;16(1):76.

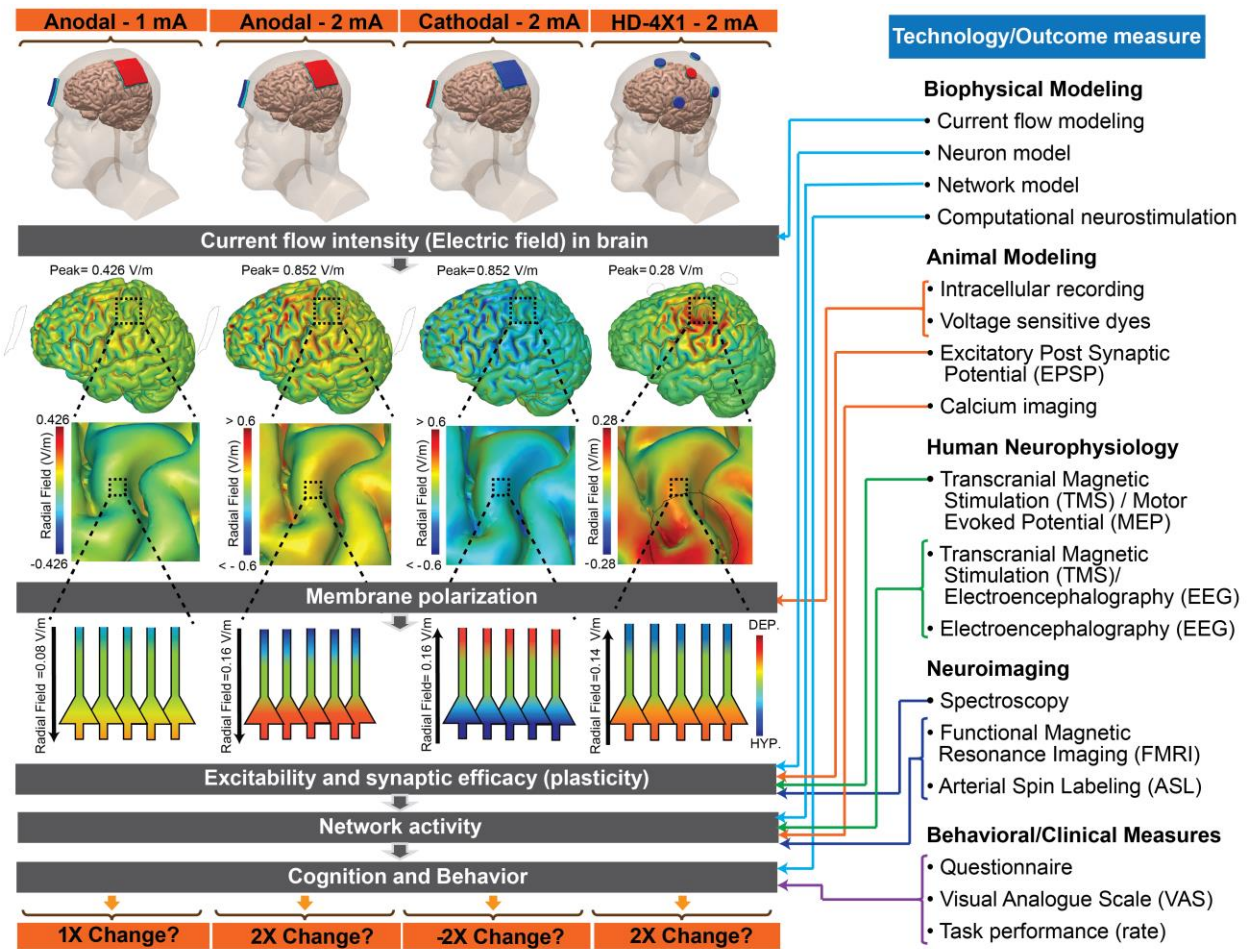
785 [111] Buch ER, Santarnecchi E, Antal A, Born J, Celnik PA, Classen J, et al. Effects of tDCS on motor
786 learning and memory formation: a consensus and critical position paper. *Clin Neurophysiol*
787 2017;128(4):589-603.

788 [112] Weinberger AB, Green AE, Chrysikou EG. Using Transcranial Direct Current Stimulation to
789 Enhance Creative Cognition: Interactions between Task, Polarity, and Stimulation Site. *Front Hum*
790 *Neurosci* 2017;11.

- 791 [113] Woods A, Antal A, Bikson M, Boggio PS, Brunoni A, Celnik P, et al. A technical guide to tDCS,
792 and related non-invasive brain stimulation tools. *Clin Neurophysiol* 2016;127(2):1031-48.
- 793 [114] Bestmann S, de Berker AO, Bonaiuto J. Understanding the behavioural consequences of
794 noninvasive brain stimulation. *Trends Cogn Sci* 2015;19(1):13-20.
- 795 [115] Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled,
796 phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal
797 cord injury. *Pain* 2006;122(1):197-209.
- 798 [116] Shah-Basak PP, Norise C, Garcia G, Torres J, Faseyitan O, Hamilton RH. Individualized
799 treatment with transcranial direct current stimulation in patients with chronic non-fluent aphasia due to
800 stroke. *Front Hum Neurosci* 2015;9:201.
- 801 [117] Bikson M, Rahman A. Origins of specificity during tDCS: anatomical, activity-selective, and
802 input-bias mechanisms. *Front Hum Neurosci* 2013;7:688.
- 803 [118] López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-del-Olmo M. Inter-individual
804 variability in response to non-invasive brain stimulation paradigms. *Brain Stimul* 2014;7(3):372-80.

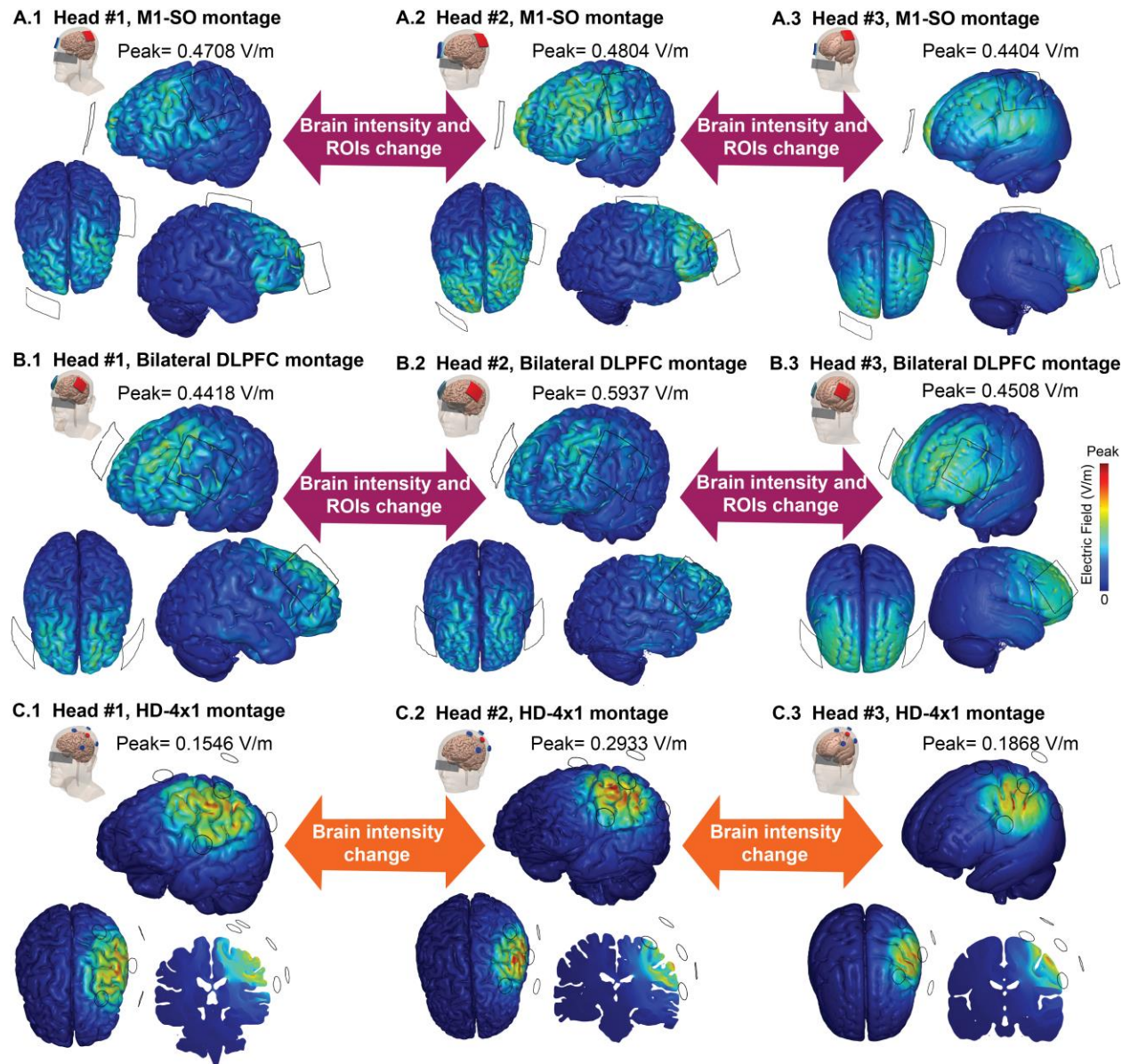
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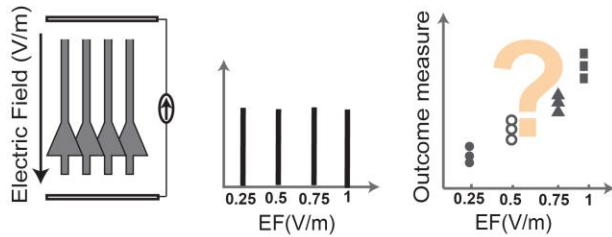
809 **Figure 1:** An aggregate linear tDCS intensity dose response requires linear input-output function in each scale from a
 810 single neuron to local neuronal circuits and plasticity, to large scale interconnected neuronal networks and ultimately
 811 behavior and task performance. Induced electric field (or current intensity) in the brain increases linearly with applied
 812 stimulation current. In well-controlled, in-vitro experiments, increased membrane polarization can be reasonably
 813 assumed with increasing tDCS intensity but in an active brain, nonlinear and complex behavior is more likely.
 814 Different experimental, modeling and imaging techniques assist to map tDCS modulation in specific scales.



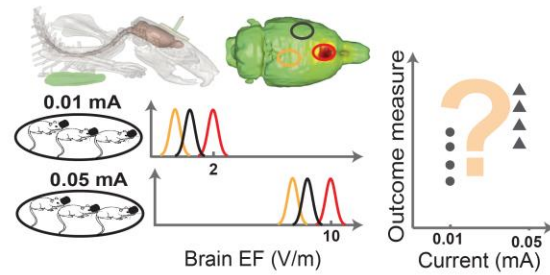
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816 **Figure 2:** Cortical electric field intensity and pattern across two different subjects (Head #1, Head #2) and standard
 817 averaged head (Head #3) for 1 mA stimulation using different electrode montages. A: anode (red) over left M1 and
 818 cathode (blue) over contralateral-supraorbital across different heads (A.1, A.2, A.3). B: bilateral DLPFC, anode (red)
 819 over left DLPFC (F3, EEG standard system) and cathode (blue) over right DLPFC (F4, EEG standard system) across
 820 different heads (B.1, B.2, B.3). Conventional pad electrodes deliver current to multiple brain regions that varies across
 821 subjects. For HD-tDCS configuration, C: anode (red) over M1 and cathodes (blue) with 6 mm center to center distance
 822 from anode for three different heads (C.1, C.2, C.3). ROI, region of interest.

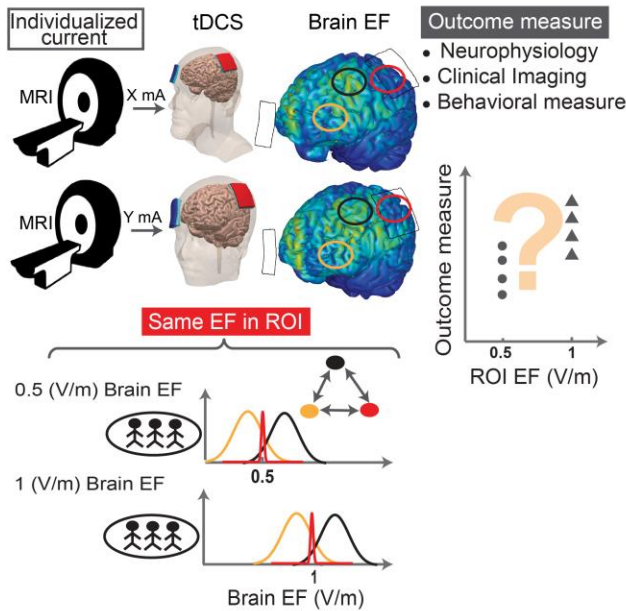
A.1 Fixed Electric Field (in-vitro animal model)



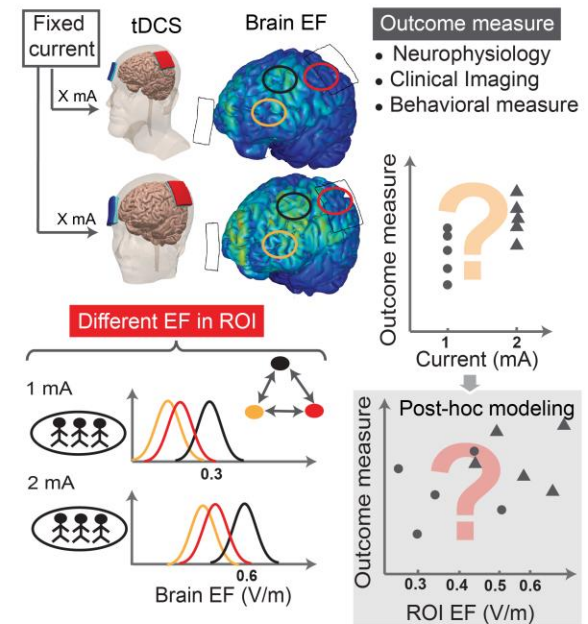
A.2 Fixed current over skull (in-vivo animal model)



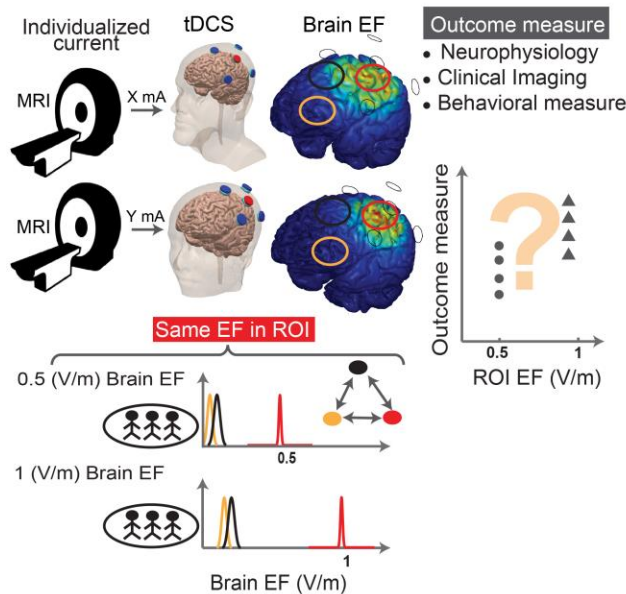
B.1 Fixed Electric field inside brain (conventional electrodes)



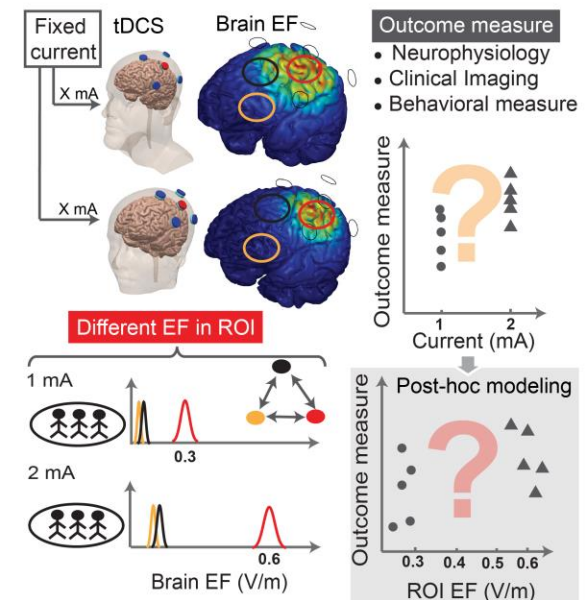
B.2 Fixed stimulator output (conventional electrodes)



C.1 Fixed Electric field inside brain (HD-electrodes)



C.2 Fixed stimulator output (HD-electrodes)



824 **Figure 3:** Experimental design of dose-response studies in animal and man. 6 experimental paradigms are illustrated,
825 2 in animal and 4 in human trials. Approaches where electric field is controlled (left column) are contrasted with
826 approaches where applied current is fixed (right column). In human trial panels, the use of anatomical MRI scans is
827 illustrated by a MRI cartoon. The use of a tDCS or HD-tDCS montage is illustrated on two semi-transparent head.
828 Predicted electric field are shown in false color on the cortex. In each case, one or more outcome measures would be
829 correlated against electric field in the ROI or the applied current, with the question-mark indicating a monotonic
830 relationship is not necessarily established. The nominal ROI may be assumed to be “under” one electrode (red circle)
831 with other brain region considered (yellow and black circles). In each panel, a simplified representation of the electric
832 field distribution across a population (three stick figure cartoon) includes three brain regions (the nominal ROI in red,
833 and other brain regions in yellow, black). These regions may be interconnected such that the outcome measure can
834 reflect aggregate network stimulation. (A.1) In vitro animal brain slice models are stimulated with a uniform electric
835 field. The electric field can be increased and an outcome measure recorded. Few in vitro studies applied several
836 increments of electric magnitude in the tDCS range (<1 V/m). (A.2) In vivo animal models apply a fixed current with
837 an epi-cranial electrode which results is animal-specific electric field in the ROI (red) and varied electric fields in
838 other brain regions (Yellow, Black). Increasing the applied current increases all the electric field in each brain region
839 proportionally. Electric field in animal models will be dramatically above the human case when comparable currents
840 are applied. An outcome measures is recorded at varied applied current levels. (B.1) Using conventional electrode
841 pads, controlled electric field intensity can be applied to a ROI in human trials by varying the applied current in each
842 individual to generate a fixed electric field at the ROI. They require individual current flow modeling. The electric
843 fields in other brain regions are not controlled and so vary across individuals and may be higher than in the ROI. An
844 outcome measures is recorded at varied controlled ROI electric fields. (B.2) Using conventional electrode pads, a
845 fixed current is applied across subjects for each dose, which results in variable electric field at the ROI as well as at
846 other brain regions. For each subject, increasing the applied current increases all the electric field in each brain region
847 proportionally. The electric field may be maximal outside the ROI. An outcome measures is recorded at varied applied
848 current. [shaded inset] Post-hoc individual model may be used to reanalyze data based on predicted electric field in
849 the ROI. This may result in some subjects in the lower-current group having a higher electric field at the ROI than
850 some subjects in the low current group. (C.1) Using the high-definition 4x1 montage, controlled intensity electric field
851 can be applied to a ROI in human trials by varying the applied current in each individual to generate a fixed electric

852 field at the ROI. The require individual current flow modeling based on MRI. Across individuals, the electric field is
 853 predicted to be focal and maximal at the ROI across stimulation intensities. An outcome measures is recorded at varied
 854 controlled ROI electric fields. (B.2) Using the high-definition 4x1 montage, fixed currents are applied across, which
 855 results in variable electric field at the ROI at each current, however, the maximal electric field remains in the ROI
 856 across individuals. For each subject, increasing the applied current increases all the electric field in each brain region
 857 proportionally, but the electric field remains minimal outside the ROI. An outcome measures is recorded at varied
 858 applied current. [shaded inset] Post-hoc individual model may be used to reanalyze data based on predicted electric
 859 field in the ROI. This may result in some subjects in the lower-current group having a higher electric field at the ROI
 860 than some subjects in the low current group.

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863 **Table 1:** Open questions on dose-response

<ul style="list-style-type: none"> - Has the scale of research on tDCS efficacy outstripped understanding of dose response? - To what extent can (canonical) findings on dose-response in the resting brain support response during a behavioral task, where specific brain regions are activated therefore changing their susceptibility to stimulation? - To what extent could non-monotonic dose response, which is dependent on individual anatomy and subject to interactions with brain state (e.g. task engagement), lead to false-negatives?
<p>The limited work on tDCS dose response had typically applied a straightforward model to measure a response with increased tDCS intensity (e.g. from 1 to 2 mA).</p> <ul style="list-style-type: none"> - To what extent is this approach subject to assumptions about the spatial extent of current flow? - Could not accounting for inter-individual anatomical variability in such cases lead to false-negatives? - Could inter-individual variations in the intensity of current delivered to the brain combined with a non-monotonic response of the brain lead to false-negatives? - How can the assumptions, implicit in conventional dose-testing studies, be made more explicit?
<ul style="list-style-type: none"> - In dose response studies, can computational models be used to retrospectively predict brain current intensity across individuals for a fixed applied current?

- Can the above retrospectively and prospective use of computational models reduce variability and/or increase effect size in tDCS efficacy trials?

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