

Transcranial Electrical Stimulation Motor Threshold Combined with Reverse-Calculated Electric Field Modeling Can Determine Individualized tDCS Dosage

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tDCS Dosing

Abstract

Background: Unique amongst brain stimulation tools, transcranial direct current stimulation (tDCS) currently lacks an easy method for individualizing dosage.

Objective: Can one individually dose tDCS? We developed a novel method of reverse-calculating electric-field (E-field) models based on Magnetic Resonance Imaging (MRI) scans that can determine individualized tDCS dose. We also sought to develop an MRI-free method of individualizing tDCS dose by measuring transcranial magnetic stimulation (TMS) motor threshold (MT) and single pulse, suprathreshold transcranial electrical stimulation (TES) MT and regressing it against E-field modeling.

Methods: In 29 healthy adults, we acquired TMS MT, TES MT, and structural MRI scans with a fiducial marking the motor hotspot. We then computed a “reverse-calculated tDCS dose” of tDCS applied at the scalp needed to cause a 1.00V/m E-field at the cortex. Finally, we examined whether the predicted E-field values correlated with each participant’s measured TMS MT or TES MT.

Results: We were able to determine a reverse-calculated tDCS dose for each participant. The Transcranial **Electrical** Stimulation MT, but not the Transcranial **Magnetic** Stimulation MT, significantly correlated with the calculated tDCS dose determined by E-field modeling ($R^2 = 0.509$, $p < 0.001$).

Conclusions: Reverse-calculation E-field modeling, alone or in combination with TES MT, shows promise as a method to individualize tDCS dose. The large range of the reverse-calculated tDCS doses between subjects underscores the likely need to individualize tDCS dose. If these results are confirmed in future studies, TES MT may evolve into an inexpensive and quick method to individualize tDCS dose.

tDCS Dosing

1 **Introduction**

2 Transcranial direct current stimulation (tDCS) is an appealing brain stimulation method
3 due to its efficacy in treating multiple neurological and psychiatric conditions(1-4), relatively
4 cheap cost(5, 6), excellent safety profile(7), and ease of use that could lead to self-
5 administration(7-9). However, tDCS currently does not have a method or biomarker to confirm
6 that stimulation is reaching the cortex or to individualize dose. A typical tDCS study applies a
7 weak uniform electrical current (typically 1-2mA for 20 minutes)(10), often paired with a
8 behavioral task, that may underdose some individuals and be a cause of mixed findings in the
9 field(11-21). Determining a method of individualizing tDCS dosage is important as it would likely
10 inform the experimental design and interpretation of tDCS studies, probably improve the effect
11 size, and allow for more rigorous clinical and investigational use.

12 Very few studies have examined if there is a way to individualize tDCS dosage. One
13 potential method could be to use electric-field (E-field) modeling combined with a
14 neurophysiological measurement such as transcranial magnetic stimulation (TMS) motor
15 threshold (MT)(22). Researchers have shown that TMS MT correlates with the E-field produced
16 by 1mA of tDCS(22). However, no study has yet explored how to use E-field modeling and a
17 neurophysiological measurement to prospectively individualize tDCS dosage; studies to date
18 have used retrospective tDCS E-field modeling or for only a uniform dose such as 1mA.

19 To prospectively individualize tDCS dosage using E-field modeling, a first step is to
20 decide upon a desired E-field threshold at the cortex. Currently, there is no consensus about the
21 amount of stimulation it would take to excite cortical tissue using tDCS, likely owing to different
22 neuronal cell types firing at varying thresholds and difficulty with assessing such a threshold in
23 vivo(23). A controversial study by Vöröslakos and colleagues (2018) used implanted electrodes
24 in human cadavers and anesthetized rats to measure the intracortical E-fields produced by
25 tDCS from electrodes on the scalp(24). While many tDCS researchers disagree with the
26 conclusions of the study, Vöröslakos and colleagues determined that an E-field of at least

tDCS Dosing

27 1mV/mm (equivalent to 1V/m) at the cortex is required to affect neuronal spiking and
28 subthreshold currents; they further estimate that it would likely take 4-6mA of tDCS current to
29 produce E-fields of the 1mV/mm magnitude(24). In this study, we chose to use the 1V/m
30 threshold that was informed by Vöröslakos et al.'s study. An additional benefit of using 1V/m is
31 that it is easily scalable to the desired E-field by multiplication or division. For example, if 0.5V/m
32 is the desired threshold to individualize tDCS dosage to, the calculated tDCS dose to produce
33 1V/m would be halved.

34 We aimed to develop a novel method of using E-field modeling to determine an
35 individualized, "reverse-calculated tDCS dose" to produce an E-field threshold of 1.00V/m that
36 could easily be scaled up or down. We correlated the theoretical reverse-calculated tDCS dose
37 with acquired values of TMS MT and transcranial electrical stimulation (TES) MT to determine if
38 a neurophysiological measure could be used to predict individualized reverse-calculated tDCS
39 dose. We hypothesized that TMS MT or TES MT would correlate with reverse-calculated tDCS
40 dose for a 1.00V/m E-field and could be used in the future to individually titrate tDCS dosage to
41 any desired threshold.

tDCS Dosing

42 **Materials and Methods**

43 Study Overview

44 We enrolled 30 healthy participants (15 women, mean age = 26.9, SD = 9.1) in this two
45 visit IRB-approved study. One participant dropped out prior to receiving the MRI scan, so our
46 final sample size was 29. Each participant gave written, informed consent before starting the
47 experimental protocol. In Visit 1, we acquired a resting TMS MT for each participant by
48 stimulating the left motor cortex and recording motor evoked potentials (MEPs) in a standard,
49 closed-loop TMS MT acquisition protocol. We used three electrodes on the contralateral right
50 hand, combined with Spike2 software, to record MEPs. We defined an MEP as having a peak-
51 to-peak amplitude greater or equal to 0.05mV. Parametric Estimation via Sequential Testing
52 (PEST) software was used to help optimally determine the TMS MT in as few pulses as
53 possible(25).

54 Following TMS MT acquisition, we then acquired an active TES MT for each participant
55 by placing an anodal tab electrode (Natus Neurology, Inc., Pleasanton, CA, USA; rectangular
56 with dimensions of 35 x 20mm) over the TMS motor hotspot and a cathodal ground plate
57 electrode (Natus Neurology, Inc., Pleasanton, CA, USA; rectangular with area = 55 x 42mm)
58 over the left deltoid (**See Figure 1, Supplemental Material S1, and Supplemental Video for a**
59 **detailed description of the TES procedure**). Briefly, participants were instructed to make a
60 “thumbs-up” sign with their contralateral right hands to active the motor circuit, which Merton
61 and colleagues (1982) had previously shown lowers the TES MT by approximately 20%(26).
62 Single, suprathreshold TES pulses were delivered using a constant current stimulator (Digitimer
63 DS7A, Letchworth Garden City, England, UK). With a pulse width of 200µs, a maximum voltage
64 of 400V, monophasic waveform, and an initial stimulation intensity of 58.0mA, we used a
65 modified PEST program to determine the TES MT using only 5 pulses and were able to acquire
66 a relatively painless TES MT for each participant (**See Supplemental Material S2 for painfulness**
67 **and tolerability ratings**).

tDCS Dosing

68 In Visit 2, each participant underwent a structural magnetic resonance imaging (MRI)
69 scan. A vitamin E capsule was used as a fiducial to mark each participant's previously
70 determined scalp target for the TMS/TES MT. This allowed the motor hotspot location to later be
71 visualized in MRICro.

72 Preparing MRI Scans for E-Field Modeling

73 We used the MRICro program to visualize the fiducial marking the left hemispheric motor
74 hotspot location and noted the X, Y, and Z coordinates for the fiducial location (**See Figure 2**).
75 In addition, we approximated the cathodal electrode location over the left deltoid by finding the
76 lowest location on the left shoulder visible on the MRI scan (**See Figure 1**). For our E-field
77 modeling, we used "Realistic vOlumetric-Approach to Simulate Transcranial Electric
78 Stimulation" (ROAST)" software(27), which allowed us to use the individualized electrode
79 placements, sizes, and orientations used to determine TES MT.

80 Prospective ROAST E-Field Modeling

81 Most tDCS E-field modeling studies use modeling to determine the E-field produced by a
82 uniform tDCS current placed on the scalp (e.g. What is the E-field produced by 2mA of
83 stimulation?). In this study, we had the opposite question: To produce an E-field of a 1.00V/m at
84 a certain spot in the cortex, what would be the individualized, reverse-calculated tDCS dose for
85 the electrode on the scalp?

86 We used ROAST V2.7 for our tDCS E-field modeling as it allowed us to customize the
87 electrode sizes and locations for each participant based on their structural MRI scans(27). We
88 customized the TES pad electrode sizes (Anode: 35mm x 20mm x 3mm; Cathode: 55mm x
89 42mm x 3mm), locations (left motor hotspot, left deltoid), and orientations (anterior-to-posterior)
90 to reproduce the TES montage in the ROAST code using MATLAB R2015a.

91 ROAST E-Field Modeling Methodology- Within Individual Analysis

92 We sought to determine the reverse-calculated tDCS dose that would be necessary to
93 cause a 1.00V/m E-field at the cortex in each individual by reverse-calculating the ROAST

tDCS Dosing

94 model by computing four E-field models per participant. Using the exact electrode locations
95 used to acquire TES MT, we modeled the E-fields produced from tDCS currents of: 1mA, 3mA,
96 5mA, and 7mA. We plotted these E-field estimates (in V/m) along the X-axis against the tDCS
97 current input on the Y-axis. We also included the point of 0mA input producing a 0V/m E-field for
98 a total of 5 points in the linear regression.

99 To determine the E-field produced in each model, we measured the E-field at the voxel
100 directly underneath the center of the anodal electrode that was placed over the left motor
101 hotspot. We calculated a linear regression for this intra-individual model and solved the linear
102 equation for the “reverse-calculated tDCS dose” that would produce exactly a 1.00V/m E-field
103 for that subject at that location. We then computed a fifth ROAST model at this reverse-
104 calculated tDCS dose to confirm that the stimulation input produced the 1.00V/m E-field, and
105 accepted values with a range of 0.99-1.01V/m. All reverse-calculated models produced an E-
106 field value in this range.

107 Our reverse computation may seem overly elaborate, as theoretically, the electric field is
108 linear with applied current. You should be able to run the model (for a given montage and head)
109 for any current (say 1mA). With multiplication (e.g. no regression) you could then scale the
110 current to produce any desired electric field. This ‘shortcut’ may prove true for future work, and
111 general values. However, the reverse-calculated dose that emerges from the individualized
112 linear model by putting in different current amplitudes is not exactly linear, and we sought in this
113 paper to rigorously test for these assumptions. In the future researchers and clinicians might be
114 able to use one model and scale this up or down as a method of reverse-calculating tDCS dose
115 *ROAST E-Field Modeling x TMS MT and TES MT Methodology- Group Level Analyses*

116 Following E-field modeling, we plotted each individual’s reverse-calculated tDCS dose
117 against their measured TMS MT and used a group level linear regression to determine the
118 relationship between TMS MT and reverse-calculated tDCS dose (**Figure 3**). We used this
119 same method to then assess the relationship between TES MT and the reverse-calculated

tDCS Dosing

- 120 tDCS dose in a group level E-Field Model x TES MT regression (**Figures 4**). All statistical
121 analyses were conducted in SPSS 25.0 (Armonk, NY: IBM Corp).

tDCS Dosing

122 **Results**

123 TMS and TES Motor Threshold (MT) Descriptive Statistics

124 The mean TMS MT was 40.19% of machine output (SD = 12.7%, range = 20-67.3%).

125 The mean TES MT was 61.35mA (SD = 14.91mA, range = 37.1-82.35mA).

126 Reverse-calculated tDCS Dose: Actual Electrode Placement and Sizes

127 The mean reverse-calculated tDCS dose to produce a 1.00V/m E-field in the motor
128 cortex using actual electrode placements was 6.38mA (SD = 1.34mA, range = 3.86 to
129 10.21mA).

130 TMS MT x Reverse-calculated tDCS Dose Linear Regression

131 This linear regression evaluated the relationship between TMS MT and reverse-
132 calculated tDCS dose determined from the same electrode placement and sizes used for
133 acquiring the TES MT (mean reverse-calculated tDCS dose = 6.38mA, SD = 1.34mA, range =
134 3.86 to 10.21mA). TMS MT did not statistically predict tDCS dose variance, $F(1,27) = 0.813$, R^2
135 = 0.029, $p = 0.375$ (**See Figure 3**).

136 TES MT x Reverse-calculated tDCS Dose Linear Regression

138 This regression model used the same electrode placement and sizes used to determine
139 the TES MT that were previously used in the TMS MT regression in **Figure 3** (mean reverse-
140 calculated tDCS dose = 6.38mA, SD = 1.34mA, range = 3.86 to 10.21mA). In this regression,
141 TES MT significantly predicted 50.9% of the reverse-calculated tDCS dose variance to produce
142 a 1.00V/m E-field, $F(1,27) = 27.985$, $R^2 = 0.509$, $p < 0.001$ (**See Figure 4**).

143 The equation for the linear regression is: **Reverse-calculated tDCS Dose = 0.0643 ***
144 **TES MT + 2.4319**. Thus, measuring a new TES MT and plugging the value into the formula
145 above would allow one to prospectively determine an individual's reverse-calculated tDCS dose.
146 For example, if an individual had a TES MT of 60mA, the reverse-calculated tDCS dose to
147 produce a 1.00V/m E-field at their motor cortex would be 6.29mA. Notably, this reverse-

tDCS Dosing

148 calculated tDCS dose for a 1.00V/m E-field at the cortex is easily scalable. For example, the
149 reverse-calculated tDCS dose for a 0.50V/m E-field in the same individual would be: $6.29\text{mA} \times$
150 $0.5 = 3.145\text{mA}$.

151 TMS MT x TES MT Linear Regression

152 We examined the relationship between TMS MT and TES MT by comparing the
153 measured values for each individual in a linear regression. These values did not significantly
154 correlate, $F(1,27) = 2.95$, $R^2 = 0.099$, $p = 0.097$.

tDCS Dosing

155 **Discussion**

156 We conducted a study in 29 healthy individuals in which we used both TMS and TES
157 motor thresholds (MT), combined with anatomical neuroimaging and E-field modelling to
158 determine an individualized dosing paradigm for tDCS. This E-field modeling paradigm, was
159 used to determine an individual's reverse-calculated tDCS dose to produce an E-field of
160 1.00V/m. We found that an individual's transcranial **electrical** stimulation (TES) MT predicted
161 the reverse-calculated tDCS dose needed to produce a 1.00V/m E-field at the cortex. A linear
162 regression model using the same electrode sizes and positions as our TES MT acquisition
163 predicted 50.9% of the reverse-calculated tDCS dose variance across our sample.

164 In contrast, a person's transcranial **magnetic** stimulation (TMS) MT did not correlate
165 with the reverse-calculated tDCS dose to produce a 1.00V/m E-field at the cortex. It is unclear
166 why TES MT but not TMS MT correlates with the modelled tDCS dose, but it is likely that the
167 tDCS modeling better captures electrical energy current than that produced by TMS due to
168 differing mechanisms. Our finding that TMS MT did not correlate with TES MT corroborates the
169 idea that TMS MT may not predict reverse-calculated tDCS dose due to a different mechanism
170 (electromagnetic rather than electrical stimulation).

171 This study suggests several points. First, it is possible to significantly predict
172 approximately 50% of reverse-calculated tDCS dose variance across a relatively young and
173 healthy cohort of participants by combining TES MT and ROAST E-field modeling. While we
174 acquired and analyzed structural MRI scans for each participant in this study, in the future this
175 regression approach could potentially allow TES MT acquisition alone to determine an
176 individual's reverse-calculated tDCS dose. However, before this regression comparing TES MT
177 and reverse-calculated tDCS dose can be used widely, our results need to be tested for
178 replication and then shown to be valid in some form of a tDCS study measuring behavioral
179 effects.

tDCS Dosing

180 Second, the reverse-calculated tDCS dose to cause an E-field at a particular threshold
181 at the cortex varies widely between individuals (3.86 to 10.21mA to produce a 1.00V/m E-field at
182 the cortex). This variability in reverse-calculated tDCS dose is substantial. To illustrate the range
183 of dosage, the individual needing the highest reverse-calculated tDCS dose (10.21mA) in our
184 actual electrode position and size model would need a reverse-calculated tDCS dose that is
185 265% higher than the individual who needed the lowest reverse-calculated tDCS dose
186 (3.86mA). In addition, the inter-individual variance exists regardless of the intended threshold in
187 any region of the brain. For example, in order to produce a 1.00V/m induced electrical field at
188 the motor cortex, the range of tDCS dose needed was from 3.86 to 10.21 mA (average 6.38 mA
189 tDCS dose at scalp). If we moved the entire scale average to instead average 2.0mA at the
190 scalp, the needed individualized range remains 1.21-3.22mA across the sample. If the average
191 dose of 2.0mA were applied uniformly (similarly to how a uniform dose is applied in every extant
192 tDCS study), it would underdose any individual needing above 2.0mA, particularly the person
193 requiring 3.22mA. Taken in sum, our E-field modeling corroborates the idea that individualized
194 tDCS dose is needed for consistent dosing across individuals and studies.

195 Third, and perhaps controversially, if a 1.00V/m E-field threshold is necessary to cause a
196 spike in neuronal firing, the results from this study support the idea that a uniform 1-2mA tDCS
197 dose is likely insufficient to reach the cortex with a large effect in many participants. While
198 acknowledging that there may actually be some increases in neuronal resting membrane
199 potential at lower than 1.00V/m, our models using this threshold showed that no participant's
200 reverse-calculated tDCS dose was below 3.86mA and the average reverse-calculated tDCS
201 dose was 6.38mA. tDCS likely has effects at intensities below the 1.00V/m assumption we
202 used, but depending on the reverse-calculated threshold, these results suggest that some, if not
203 many, individuals are underdosed when uniform doses are used.

tDCS Dosing

204 Limitations

205 There were several limitations of this study. Using E-field modeling, even when it has
206 been validated using intracranial recordings, is inherently theoretical. In addition, the method of
207 reverse-calculating tDCS dose can be further refined. While ROAST E-field modeling nicely
208 accounts for many potential co-factors such as scalp-to-cortex distance and tissue conductivity,
209 there may be other factors that influence response to tDCS, even if the stimulation reaches the
210 cortex. Our regression value of $R^2 = 0.509$ in **Figure 4** suggests that using TES MT to
211 determine an individualized reverse-calculated tDCS dose for each participant can predict
212 slightly more than 50% of the dose variance. This is a major step forward from accounting for
213 0% of dose variance in all extant tDCS studies that use uniform doses of current. However, this
214 also means that the source of approximately 50% of the dose variance remains to be
215 determined. A future dose-response study would help to elucidate if individualized dose
216 improves response to tDCS and what other factors may influence reverse-calculated tDCS
217 dose. The relationship between TES MT and reverse-calculated tDCS dose might also change
218 outside of the motor cortex or with different electrode montages (e.g. left M1-supraorbital) and
219 are ongoing areas of research in our lab.

220 Lastly, it remains unclear what E-field magnitude to target when calculating the reverse-
221 calculated tDCS dose. Based on the existing literature(24) and for ease of scalability to a
222 desired E-field threshold, we reverse-calculated an individualized tDCS dose to produce a
223 1.00V/m E-field at the cortex for each person. However, it is possible that the 1.00V/m E-field
224 requirement for an increase in neuronal resting potential determined from rodent and human
225 cadaver studies would not scale up to humans or may differ in live human tissue(28). In fact,
226 many tDCS researchers disagree with this 1.00V/m E-field threshold. Thus, using the
227 combination of TES MT and reverse-calculation E-field modeling to individually dose tDCS
228 could potentially be even more informative as the field refines its understanding about the

tDCS Dosing

229 minimally necessary E-field magnitude needed to excite cortical tissue, and then scaling our
230 findings up or down to fit calculate the true reverse-calculated tDCS dosage for each person.

231 *Conclusions*

232 TES MT is feasible and tolerable. This value, either combined with reverse-calculated E-
233 field modeling or stand alone, can be used to determine a theoretical reverse-calculated tDCS
234 dose for stimulation to reach the cortex of each individual. Our statistical model comparing TES
235 MT to reverse-calculated tDCS dose can be used to individually dose tDCS, predicting
236 approximately 50% of the dose variance in tDCS studies. Moreover, these regressions reveal
237 the wide range (i.e. 3.86 to 10.21mA) between participants, underscoring the need to further
238 develop and evaluate the utility of TES MT combined with E-field modeling for dosing tDCS.

tDCS Dosing

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Figure Legends

Figure 1: TES Electrode Set-Up. **1A:** Experimental set-up with labeled devices and electrodes. **1B:** A picture of the constant current stimulator (Digitimer DS7A) used to acquire TES MT. **1C:** PEST program window showing an example in which 5 pulses of TES determined a TES MT of 50mA.

Figure 2: ROAST E-Field Modeling Pipeline for One Participant (1cm Diameter Circular Electrodes). **2A:** Structural MRI with an arrow pointing at the fiducial on the scalp indicating the motor hotspot coordinates (visualized in MRICroGL). **2B:** Using ROAST, an anodal electrode was placed at the left motor hotspot and the cathode was placed on the left shoulder to match the TES electrode montage. **2C:** ROAST E-field model output after skin, skull, CSF, and brain tissue segmentation. **2D/2E:** Close-up views of coronal (2D) and axial (2E) slices with arrows indicating the voxel directly underneath the center of the fiducial marking the motor hotspot. In this example, the E-field was exactly 1.00V/m at this voxel.

Figure 3: TMS MT Does Not Correlate with Reverse-Calculated tDCS Dose, $F(1,27) = 0.813$, $R^2 = 0.029$, $p = 0.375$.

Figure 4: TES MT Significantly Correlates with Reverse-Calculated tDCS Dose, $F(1,27) = 27.985$, $R^2 = 0.509$, $p < 0.001$.

tDCS Dosing

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Figure 1

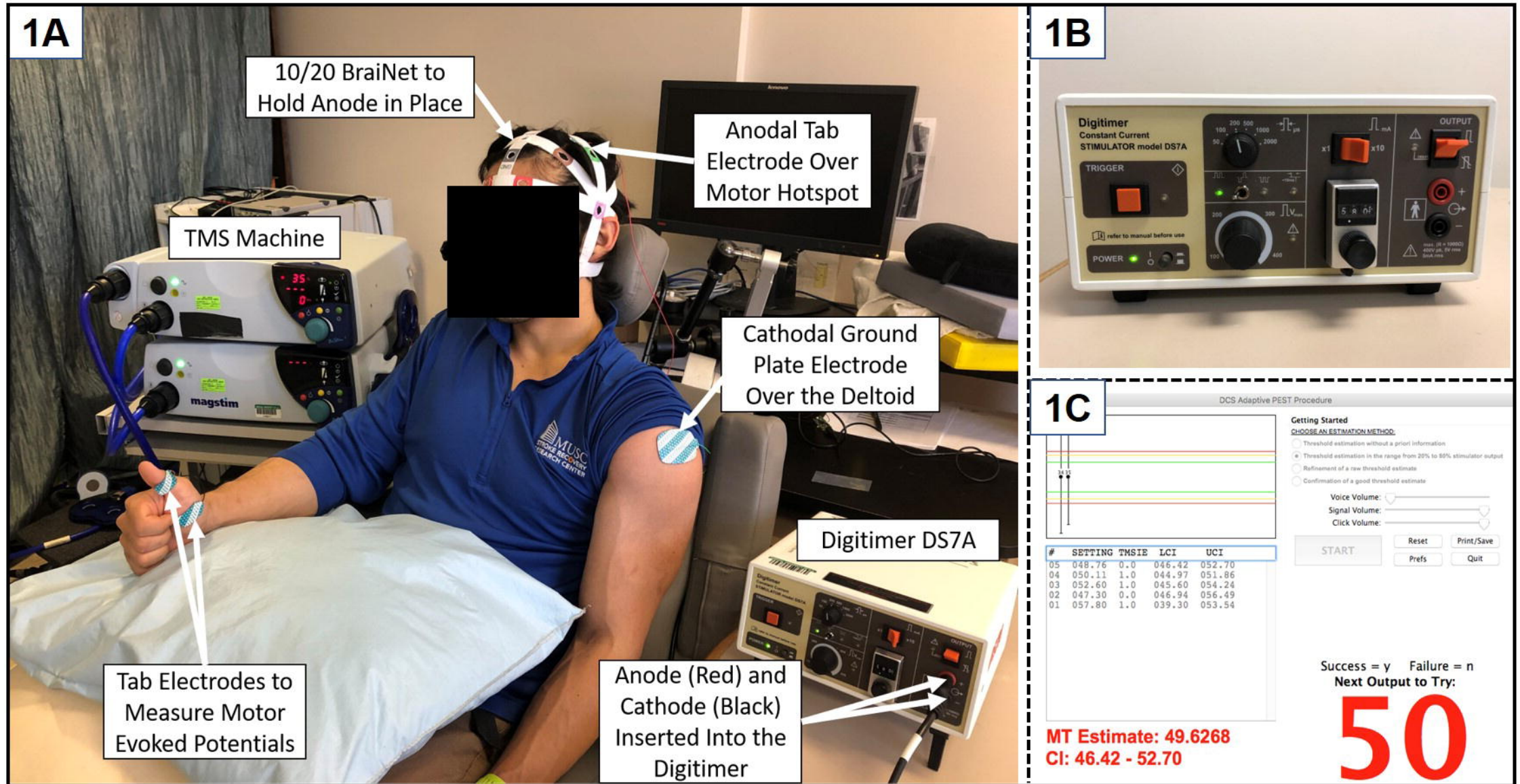
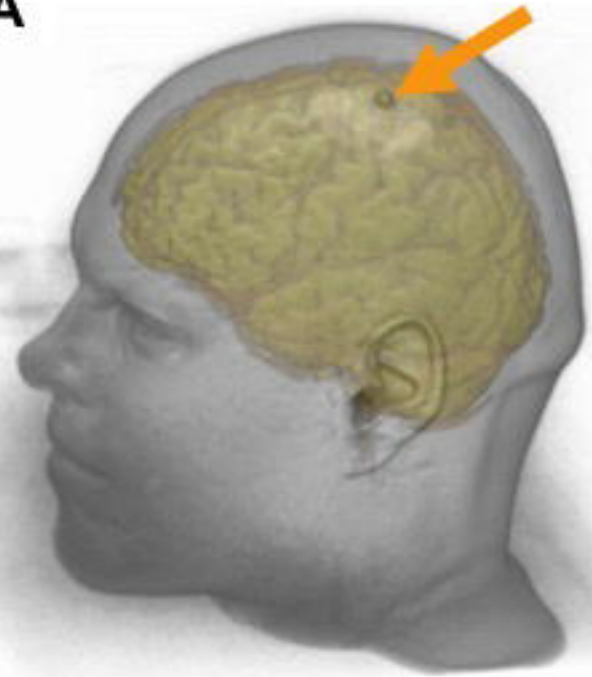
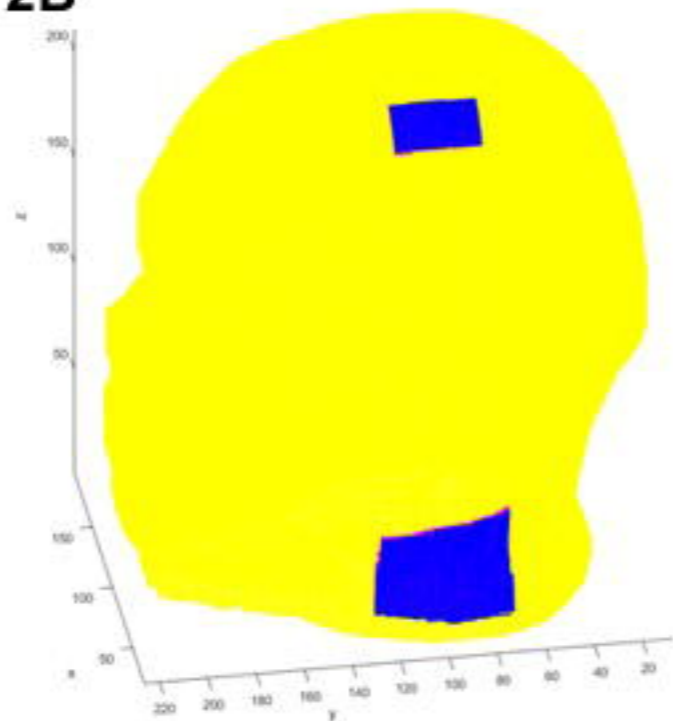


Figure 2

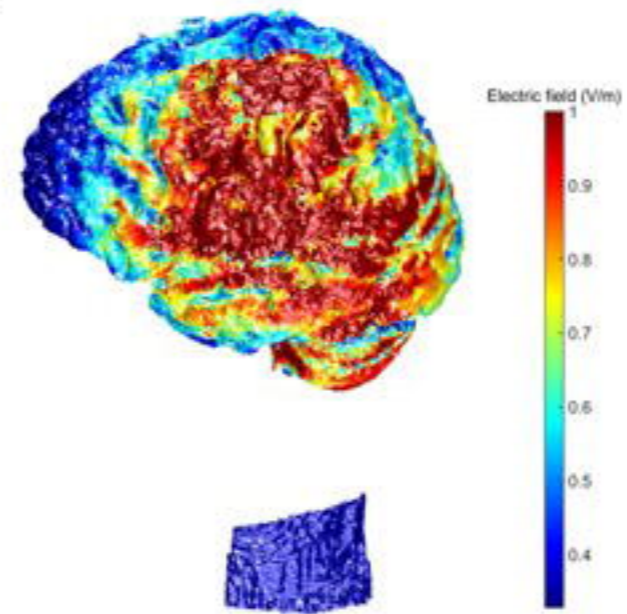
2A



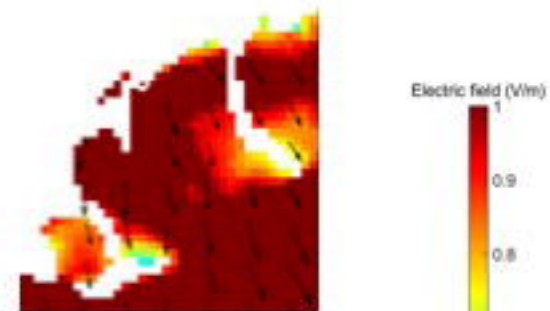
2B



2C



2D



2E

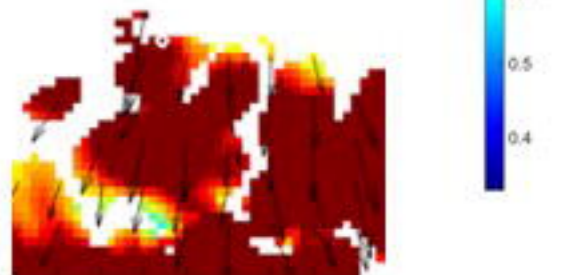


Figure 3

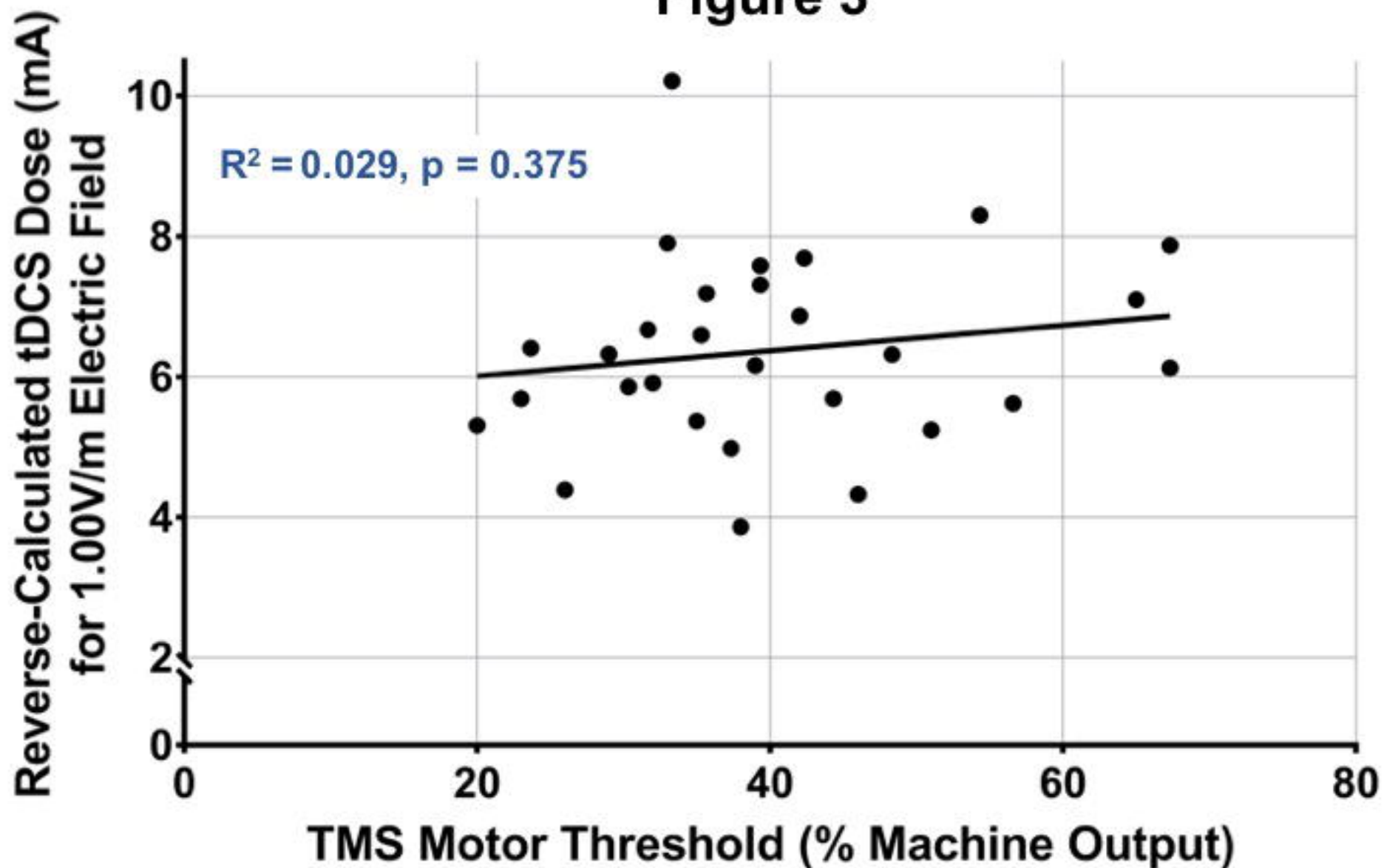


Figure 4

