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Individual differences in TMS sensitivity influence the efficacy of tDCS in facilitating sensorimotor adaptation

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) can enhance cognitive function in healthy individuals, with promising applications as a therapeutic intervention. Despite this potential, variability in the efficacy of tDCS has been a considerable concern.
Objective: /Hypothesis: Given that tDCS is always applied at a set intensity, we examined whether individual differences in sensitivity to brain stimulation might be one variable that modulates the efficacy of tDCS in a motor learning task.
Methods: In the first part of the experiment, single-pulse transcranial magnetic stimulation (TMS) over primary motor cortex (M1) was used to determine each participant's resting motor threshold (rMT). This measure was used as a proxy of individual sensitivity to brain stimulation. In an experimental group of 28 participants, 2 mA tDCS was then applied during a motor learning task with the anodal electrode positioned over left M1. Another 14 participants received sham stimulation.
Results: M1-Anodal tDCS facilitated learning relative to participants who received sham stimulation. Of primary interest was a within-group analysis of the experimental group, showing that the rate of learning was positively correlated with rMT: Participants who were more sensitive to brain stimulation as operationalized by our TMS proxy (low rMT), showed faster adaptation.
Conclusions: Methodologically, the results indicate that TMS sensitivity can predict tDCS efficacy in a behavioral task, providing insight into one source of variability that may contribute to replication problems with tDCS. Theoretically, the results provide further evidence of a role of sensorimotor cortex in adaptation, with the boost from tDCS observed during acquisition.
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Introduction

Transcranial direct current stimulation, (tDCS) has great potential as a tool for non-invasive brain stimulation. tDCS has been embraced as a technique to test causal hypotheses concerning brain-behavior relationships as well as an intervention that can boost functionality across a range of task domains [1–4]. However, considerable concerns have been raised in the literature about the reliability and robustness of the effects induced by tDCS [5–7].

One factor that may impact the efficacy of tDCS is inter-individual sensitivity to tDCS. With the exception of studies that explicitly examine dose-dependent responses [8,9], tDCS practitioners use a fixed intensity of stimulation (e.g., 1 or 2 mA). This procedure ignores anatomical, physiological, and neurochemical variables that will modulate the amplitude of the E-field at the cortical surface and responsiveness of the neurons to the induced current [10,11]. This stands in striking contrast to the common practice in the TMS literature, where the stimulation level is usually determined on an individual basis.

The use of a fixed current level in tDCS studies likely leads to considerable differences in the degree of modulation of the physiological state across a group of individuals. Some studies have classified participants as either “responders” or “non-responders” [12–14], with the assumption that this classification scheme

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captures some fundamental trait difference between the groups. However, it may be that the stimulation is insufficient for the "non-responders."

We have explored an alternative approach, using TMS as a proxy for sensitivity to brain stimulation, and asking how variability in this measure is related to the efficacy of tDCS. In an archival study [15], sensitivity to brain stimulation was operationalized as the TMS stimulation level over M1 required to produce MEPs of 1 mV. Changes in corticospinal excitability following tDCS, in which the anodal electrode was positioned over M1, varied as a function of individual differences in sensitivity to TMS: Individuals with a low TMS threshold (i.e., greater sensitivity) showed a larger increase in cortico-spinal excitability following M1-Anodal tDCS.

In the present work we turn our attention to behavior, employing a sensorimotor learning task on which performance has been shown to benefit from M1-Anodal TMS [16]. Similar to our archival study [15], we used TMS to operationalize sensitivity to brain stimulation. We predicted that M1-Anodal tDCS would prove more efficacious for sensorimotor adaptation in individuals with low TMS-measured thresholds compared to individuals with high thresholds.

Materials and methods

Participants

Forty-two young adults (age: 22.2 ± 3.8 years; 18 females) participated in the study in exchange for financial compensation. All were right handed as assessed by the Edinburgh Handedness Inventory [17]. The participants were randomly assigned to the M1-Anodal (n = 28) or Sham tDCS group (n = 14). The number of participants for the Sham group was similar to that used by Galea et al. [16], allowing us to perform a between-group comparison to evaluate the impact on learning from M1-Anodal tDCS. Given our primary interest here is on individual differences in the efficacy of tDCS, we tested a larger sample in the M1-Anodal group, one that was appropriate for the planned correlational analyses. The institutional review board at UC Berkeley approved the protocol.

Experimental design and statistical analysis

Procedure

The 1.5-h session consisted of two stages (Fig. 1). In the first stage, single-pulse TMS was used to identify the participant's resting motor threshold (rMT), our proxy for sensitivity to non-invasive brain stimulation. In the second stage, the participants performed a visuomotor adaptation task with M1anodal or sham tDCS applied during the blocks of the task in which the visual feedback was perturbed (VMA task, see below).

Transcranial magnetic stimulation (TMS) threshold procedure

Single-pulse TMS was applied over left hemisphere M1 to determine the rMT for the first dorsal interosseous muscle (FDI) in the right hand. We used FDI as the target muscle given it is relatively easy to isolate and threshold values are stable across test sessions [e.g., 18–20]. Stimulation was applied using a 70 mm figure-eight coil connected to a Rapid Magstim 200 TMS system. The coil was placed tangentially on the scalp with the handle pointing backward and laterally at a 45 angle from the midline. A surface electrode (Delsys, Inc.) was used to record motor evoked potentials (MEPs) elicited by TMS. The EMG signals were amplified and bandpass filtered on-line between 20 and 450 Hz. The signals were digitized at 2000 Hz for off-line analysis.

The coil was positioned on the scalp to identify a location that produced robust MEPs in a consistent manner. Once identified, this location was marked on the scalp to ensure stability during the threshold procedure and as a reference point for the electrode placement for tDCS. The intensity of TMS (defined in terms of percentage of maximum stimulator output, MSO) was then adjusted to determine the participant's rMT, defined as the level required to evoke MEPs of at least 50 μV peak-to-peak amplitude on 5 of 10 consecutive trials.

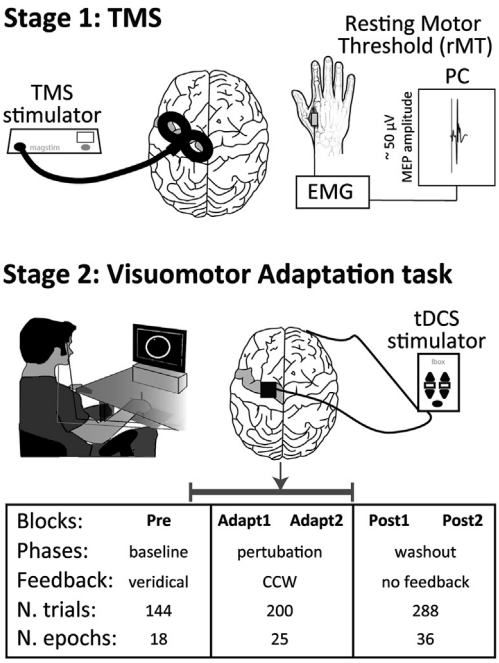

Fig. 1. Experiment Procedure. The experiment was run in a single session, divided into two stages. At the start of the experimental session (Stage 1), TMS was used to determine the resting motor threshold (rMT) for each participant, the minimum stimulation intensity required to evoke MEPs of at least 50 μV peak-to-peak amplitude in FDI. This measure served as a proxy of sensitivity to brain stimulation, under the assumption that there exists a negative correlation between rMT threshold and sensitivity to tDCS (e.g., lower rMT = higher sensitivity). Participants were then tested on a visuomotor adaptation task (Stage 2), composed of baseline, perturbation, and washout phases. In the perturbation phase, the cursor feedback was rotated 30° in the CCW direction. To examine the effects of early and late learning and forgetting the perturbation and washout phases were each divided into two blocks (Adapt1 and Adapt2; Post1 and Post2). Trials were grouped into epochs by averaging the data over eight consecutive trials (1 reach/target). tDCS stimulation (gray line) over M1 was applied during the end of the baseline phase and during most (or all) of the perturbation phase.

Visuomotor adaptation (VMA) task

For the visuomotor adaptation task, participants made center-out reaching movements to visually displayed targets, sliding a stylus with their right hand across a digitizing tablet (Wacom Technology). Movement trajectories were recorded by sampling the stylus tip at 100 Hz. The tablet was oriented horizontally and positioned 23.4 cm below a wooden frame that occluded vision of the arm. Visual stimuli were presented on a monitor oriented vertically. The system was calibrated such that there was close to a 1:1 correspondence between movement distance of the stylus and movement displacement of the cursor on the screen.

To begin each trial, a circle (3 mm, white on black background) appeared at the center of the monitor, indicating the start position. The participant moved the stylus to this location. Feedback of the stylus position was displayed as a small white cursor (feedback cursor, 2 mm) that was only visible when the hand was within 1.5 cm of the start position. After maintaining the stylus in the start position for 400 ms, a target (2 mm) appeared at one of 8 positions,

arranged radially at 10 cm diameter from the start position and separated by 45° (starting at an angle of 22.5°, with 0° defined as the position to the right of the start position). The participant was instructed to make a rapid reaching movement toward the target. To ensure that the movements were performed in an open-loop manner, the feedback cursor disappeared after the hand had moved a radial distance of 1.5 cm from the start position. On trials with visual feedback (see below), the cursor reappeared as soon as the radial distance of the hand reached 10 cm. The location of the feedback cursor was fixed at this angular position, thus providing visual feedback of the angular error. The cursor remained visible at this location for 200 ms, and was then turned off. In addition, auditory feedback was provided if the movement speed was either too fast (shorter than 225 ms) or too slow (longer than 425 ms), or if the participant stopped before reaching an amplitude of 10 cm.

The instructions emphasized that the participant should make a smooth, rapid movement, attempting to slice through the target rather than terminate the movement at the target location. After completing the reach, the participant moved his/her hand back to the start position. We did not provide specific instructions concerning whether they should hold the terminal position of the outbound movement before returning, allowing them to adopt a mode that seemed most natural. The feedback cursor was turned on when the hand was within 1.5 cm of the start position, allowing the participants to reposition their hand at the start position.

The procedure for studying visuomotor adaptation was based on the second experiment reported in Galea et al. [16]. The participant was introduced to the task with a short training phase of 20 trials, 10 with veridical feedback (i.e., location of visual feedback corresponded to stylus position) and 10 with no feedback. Following this, the participant completed 632 trials, divided into three phases. The first phase (baseline) consisted of 144 veridical feedback trials. These 144 trials were composed of 18 epochs, with each epoch including one reach to each of the eight target locations. The second phase (perturbation) was composed of 200 perturbed feedback trials (25 epochs of 8 trials each). Here the visual feedback was rotated 30° in the counter-clockwise (CCW) direction. The third phase (washout) was composed of 288 no-feedback trials (36 epochs of 8 trials each), allowing us to measure forgetting (decay towards baseline performance).

There were two short breaks during the VMA task, indicated by a message on the screen. The first occurred after trial 81, 15 trials before the onset of tDCS stimulation. The second occurred after trial 329, 15 trials before the end of the perturbation phase (and the end of tDCS stimulation). We opted to have the breaks not be coincident with the onset or offset of the perturbation since there are transient changes in performance following a break [21]. At the second break, the participant was informed that the feedback cursor would stop being visible at some point in the experiment and that she should continue, on each trial, to reach to the target. The VMA task took an average of 35.3 min (sd = 8.0) to complete.

Transcranial direct current stimulation (tDCS)

tDCS was delivered through a battery-driven constant current stimulator (Dynatron ibox). The anodal electrode was centered over the FDI hotspot of left M1, identified in the thresholding part of the experiment. The cathodal electrode was positioned above the contralateral supraorbital ridge (corresponding to position FP2 in the international 10–20 EEG system). Impedance was continually monitored and each electrode was covered by a 5 × 5 cm sponge that was kept moist with a saline solution (0.9% sodium chloride). We refer to this electrode configuration as M1-Anodal to indicate that the anodal electrode is placed over M1. As measured by single-pulse TMS, this configuration has been shown to result in an increase in corticospinal excitability lasting up to 60 min [22].

The intensity of stimulation was set at 2 mA with a 10-s ramp at the beginning and end of the stimulation period. At the beginning of the experiment, 12 ml of saline solution was applied to each sponge. Impendence was continually monitored by a voltmeter that was linked to the iontophoresis device. For the group receiving M1-Anodal tDCS, an additional 2 ml of saline was added if the impedance was too high (>5 Ω), or if the participant reported that the electrode felt itchy. To keep the methods consistent for the M1-Anodal and Sham groups, the experimenter added 2 mL of saline solution at random intervals during sham simulation. Note that, whereas participants were not informed if they were in the M1-Anodal or Sham groups, the experimenter was aware of the group assignment for each participant.

In the M1-Anodal group, tDCS stimulation started with the 97th trial of the baseline phase of the VMA task and lasted until either the end of the perturbation phase (trial 344) or 20 min, whichever came first. As in Galea et al. [16], we opted to use this conditional termination rule because we did not want stimulation to extend into the washout phase or to apply stimulation for more than 20 min. 18 participants in the M1-Anodal group completed the perturbation phase in less than 20 min (mean stimulation duration = 15.4 min, sd = 1.5 min). Five participants took longer than 20 min to complete the perturbation phase and, for these participants, the stimulator was turned off, on average, after 254.3 trials (sd = 53.4) with perturbed feedback.

In the Sham group, the onset of stimulation also began on the 97th trial of the baseline phase. The intensity of tDCS was ramped up to 2 mA over a 10 s period, and, after a 10 s hold period, ramped back down to 0 mA over a 10 s period.

Data analysis

An overview of the analysis pipeline is presented in Fig. 2. The primary measure of performance in the VMA task was angular error. When feedback was presented, angular error was defined as the angle between the target and the feedback cursor, relative to the start position. When feedback was withheld, angular error was defined as the angle formed by a line connecting the start position to the center of the target and a line connecting the start position to the position of the hand when movement amplitude reached 10 cm. Movement time (MT) was defined as the interval from when hand left start circle until amplitude reached radial distance of 10 cm.

The angular error and MT data were checked to remove trials with values more than ±3 SD from the mean, calculated on an individual basis. Since heading direction changed over the perturbation and washout phases, the outlier analysis for the angular error analysis was performed after removing the linear component in the time series, with this procedure applied separately for the perturbation and washout phases. On average, 10.0 of the 632 trials (1.6 ± 0.9%) were eliminated as outliers. Following outlier rejection, epochs were created by averaging the angular error data over eight consecutive trials (1 reach/target), resulting in a total of 79 epochs. Epochs were clustered into 5 blocks: baseline (Pre, epochs 1–18) early perturbation (Adapt1, epochs 19–31), late perturbation (Adapt2, epochs 32–43), early washout (Post1, epochs 44–61), and late washout (Post2, epochs 62–79). The perturbation and washout phases were divided into two blocks to examine the effects of early and late learning and forgetting, respectively [see 16].

Between-group analyses: In the first stage of the analysis, we performed a comparison of the M1-Anodal and Sham groups, assessing the effect of tDCS on sensorimotor adaptation. This comparison entails a replication of Galea et al. [16]; as such, we employed a similar analysis plan as that reported in their study, focusing on perturbation (Adapt1, Adapt2) and washout (Post1, Post2) blocks. We did not include the first epoch of the perturbation

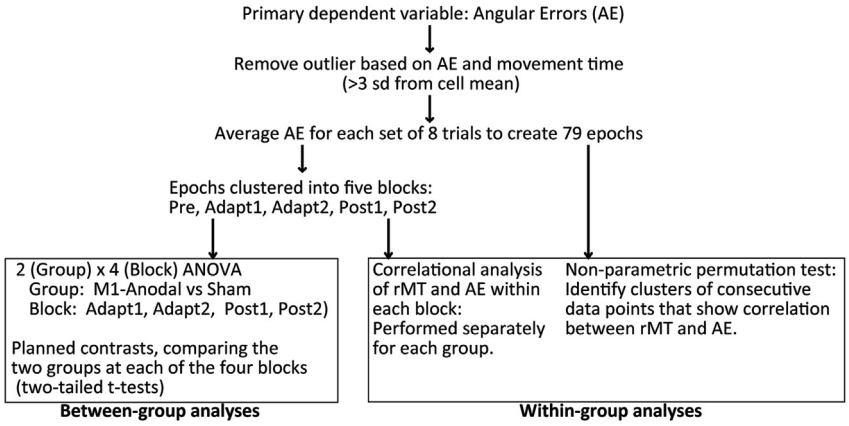

Fig. 2. Flowchart depicting the primary data analysis pipeline.

block since this would be the first time the participants experienced the rotation at each target. We subjected the mean angular error in each block to a *2 x 4 ANOVA* with factors Group (M1-Anodal/Sham) and Block (Adapt1/Adapt2/Post1/Post2). This was followed by planned contrasts comparing the effect of Group within each of the four blocks (two-tailed t-tests). Effect sizes are reported using partial eta-squared (η_p^2) for the ANOVA, and Cohen's d for the planned contrasts.

Within-group analyses: In the second stage, we turned to the primary question of this study, focusing on the data from the M1-Anodal group to evaluate whether individual sensitivity *to* brain stimulation, defined by the rMT stimulation level, was associated with the magnitude of learning-related changes from tDCS. We used two distinct analytic approaches. First, we calculated the Pearson correlation coefficient (across participants) between rMT and the mean angular error in each block. Based on our previous work [15,23], we hypothesized that participants with higher sensitivity to TMS (low rMT), would also be most sensitive to tDCS. Therefore, we predicted a positive correlation between rMT and mean angular error.

For the second analysis of individual differences, we used a non-parametric permutation test [24] that is widely employed in the analysis of multivariate data in which there are autocorrelations between sequential data points such as with EEG data [25,26]. The test is designed to identify clusters of consecutive data-points that show a significant effect, and determine the statistical significance for the cluster as a whole. This is done against a null distribution generated by randomly permuting the predictor values, and recording the largest randomly-generated cluster. Thus, this technique controls for the inflation of Type I error due to multiple comparisons and post hoc identification of clusters [24]. Although not typically applied in studies of sensorimotor learning, this approach seems highly appropriate given the continuous and autocorrelated nature of the data. It has the advantage of not limiting the analysis to arbitrary, predefined blocks.

The Pearson correlation between the error data and rMT was calculated for each of the 79 epochs and evaluated with a *t*-test. We then defined consecutive epochs (at least 2) that showed a significant correlation ($p < 0.05$) as a 'cluster', and calculated for each cluster, the sum of the t-values that were obtained for epochs in that cluster (labeled the t-sum statistic). To determine the statistical significance of a cluster, we constructed a null distribution of the t-sum statistic by performing 10,000 random permutations with the data, shuffling the rMT values across subjects in each permutation. For each shuffled dataset we repeated the same cluster-identification procedure as was done for the original data, and calculated the t-sum statistic for each of the identified clusters. Any cluster observed in the shuffled dataset is generated purely by chance. In cases where several clusters were found for a given permutation, we recorded the t-sum statistic of the cluster with the largest t-sum out of the obtained clusters. Thus, the generated null distribution is of the maximal t-sum values that are achieved by chance, reducing concerns about an increase in Type I error due to the post-hoc selection of large clusters. Each of the clusters that were originally detected in the non-shuffled data were considered statistically significant only if its t-sum was larger than 95% of the t-sums in the null distribution, corresponding to a p-value of 0.05.

We note that the Sham group was only tested as a point of comparison to verify that, overall, tDCS impacted learning, the between-group analyses described previously. Nonetheless, we performed the same analysis with this group, recognizing that we have lower power due to the reduced sample size.

Results

None of the participants reported experiencing any discomfort from the stimulation. The data from one participant in the M1-Anodal group was excluded from all of the analyses because his performance was markedly different from that of the other participants, showing minimal error after the first cycle following the perturbation and minimal change over the entire washout phase. While this could be indicative of fast learning and strong retention, it may also reflect the rapid deployment and persistent use of a re-aiming strategy.

Between-group analysis: M1-Anodal tDCS improves learning in the VMA task

In the first stage of the analysis, we tested the general effect of tDCS on learning, ignoring individual variation in rMT. Fig. 3 shows the average angular error and movement times for the M1-Anodal and Sham groups in the five blocks of the VMA task. Movement times showed a typical transient increase after the introduction of the perturbation, but did not differ between groups or interact with block (both F's < 0.25, both *p*'s > 0.60). Across groups, angular error traces displayed the typical trajectory in VMA tasks: The introduction of the perturbation led to large directional errors, which were reduced over time. Feedback (and hence the rotation) was removed during the washout phase. As expected, this led to an aftereffect, expressed as a large negative directional error. The size of this error dissipated over the course of the washout phase,

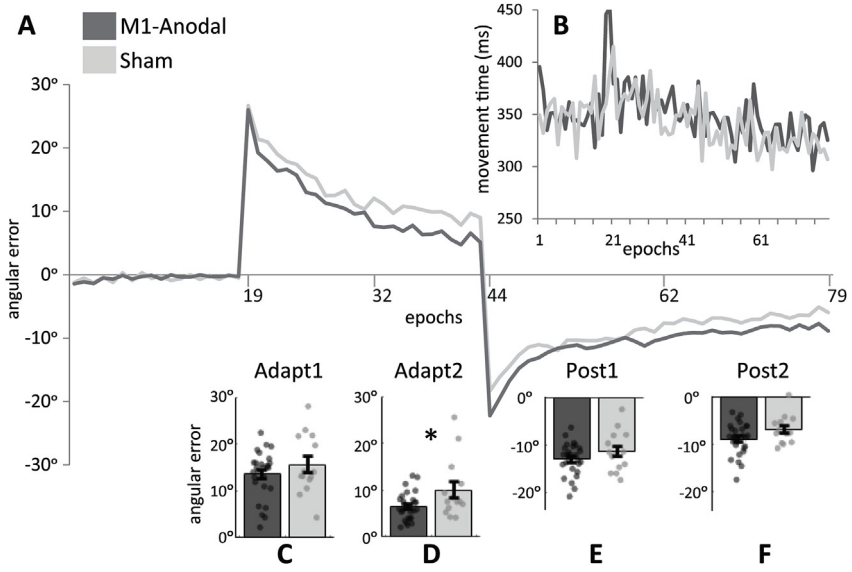

Fig. 3. Anodal tDCS over M1 induces faster learning in visuomotor adaptation. A: Angular error for each group across the reaching task. Data points show mean for epochs of eight trials (1 reach/target). Positive errors indicate movements deviated in the clockwise direction of the target, thus counteracting the perturbation during the adaptation epochs (Adapt1, Adapt2). Negative errors in the washout phases (Post1, Post2) indicate aftereffects from adaptation. B: Mean movement time, presented in the same format. C–F: Mean angular error during the early and late phases of the perturbation and washout phases. In the washout phase, the mean angular errors are shown with respect to 0, and not with respect to the end of the perturbation phase. * = $p < 0.05$.

although the aftereffect was substantial even at the end of the experiment.

The angular error scores were averaged within each block and subjected to a mixed ANOVA with factors Group (M1-Anodal/Sham) and Block (Adapt1/Adapt2/Post1/Post2). The results showed significant effects of Group ($F(1,39) = 4.21$; $p = 0.047$, $\eta_p^2 = 0.10$) and Block ($F(3,117) = 490$; $p < 0.001$, $\eta_p^2 = 0.94$) factors, but not a Group × Block interaction ($F(3,117) = 0.12$; $p = 0.72$; $\eta_p^2 = 0.02$). As can be seen in Fig. 3a, the M1-Anodal group showed a faster reduction in the angular error over the perturbation block. They also showed more angular error over the washout block, although this must be qualified given that the two groups are at different performance levels at the start of the washout block.

Following the analysis of Galea et al. [16], we conducted planned contrasts testing the effect of Group on angular error in each of the blocks following the Baseline (Fig. 3C-F). The analysis revealed that participants receiving M1-Anodal tDCS stimulation produced smaller mean angular error during the second half of the perturbation phase than those in the sham condition, indicative of faster learning (Adapt2: $t(39) = 2.39$, $p = 0.02$, Cohen's $d = 0.789$). This pattern is also present in the first half of the perturbation block, but the group difference did not approach significance (Adapt1: $t(39) = 1.68$, $p = 0.25$, Cohen's $d = 0.365$). During the washout block, the group differences were not significantly different in either half (Post1: $t(39) = 0.77$, $p = 0.20$, Cohen's $d = 0.410$; Post2: $t(39) = 1.813$, $p = 0.08$, Cohen's $d = 0.611$).

Given the differences at the end of the adaptation phase, we employed an alternative way to evaluate performance, using performance at the end of the Adapt2 stage as a baseline and measuring the amount of forgetting, relative to this baseline. For this approach, we calculated the mean heading angle over the last 5 epochs of Adapt2 and then subtracted the mean heading angle for each epoch in the Post2 stage. When retention is evaluated in this manner (Fig. 4), the results also show no group effect for either half of the washout block (Post1: $t(39) = 1.48$, $p = 0.15$, Cohen's $d = 0.473$; Post2: $t(39) = 1.135$, $p = 0.26$, Cohen's $d = 0.355$).

In summary, anodal tDCS over M1 led to improved performance on the visuomotor adaptation task, relative to sham tDCS. However,

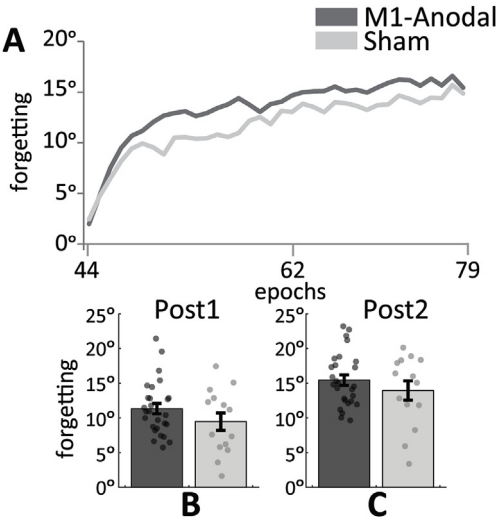

Fig. 4. Forgetting in the absence of feedback is similar for the Anodal and Sham groups. A: Change in heading angle during the washout phase, relative to a baseline (0°), set on an individual basis as the mean heading direction over the last five epochs of the perturbation phase. Data points show mean for epochs of eight trials (1 reach/target). Larger values indicate more forgetting of the adapted internal model acquired during the perturbation phase. B, C: Mean forgetting values during the early and late phases of the washout phase.

whereas Galea et al. [16] observed a difference during washout (inferred to reflect forgetting), we observed a boost in performance from tDCS during the perturbation phase.

Within-group analysis: variation in sensitivity to TMS influences the efficacy of tDCS

The main goal of the study was to examine the relationship between sensitivity to TMS and efficacy of M1-Anodal tDCS stimulation. Specifically, rMT, our proxy of sensitivity to brain stimulation, was expected to be predictive of the efficacy of tDCS.

Qualitatively, this prediction is borne out when a median split is used to divide the M1-Anodal participants into two groups based on rMT (see Fig. 5A). The high sensitivity group (low rMT) showed a faster response to the perturbation than the low sensitivity group (high rMT).

To quantitatively evaluate the sensitivity hypothesis, we used two analytic approaches. In the first approach, we correlated rMT and mean angular error, focusing on the Adapt2 block in which we had observed a group difference. The Pearson correlation was significant between angular error and rMT for the M1-Anodal group ($r = 0.42$, $t(25) = 2.28$, $p = 0.03$, Fig. 5b). Thus, sensitivity to TMS was predictive of the efficacy of tDCS in enhancing learning. Indeed, the predicted angular error for participants with a high rMT (low sensitivity) approaches the mean value observed in the Sham group.

Given that Galea et al. (2011) had observed enhanced retention at the end of washout, we also performed this analysis in the Post2 block. The correlation between angular error and rMT was not significant ($r = -0.20$, $t(25) = -1.03$, $p = 0.31$, Fig. 5c), and actually in the wrong direction assuming that higher sensitivity to brain stimulation (low rMT) should produce more error if tDCS enhances retention. We also examined the relationship between rMT and retention using the end of the Adapt2 stage as the baseline for measuring forgetting. Here we performed a multiple regression analysis in which the dependent variable was the mean angular angle in the Post2 stage, and the predictor variables were rMT and the mean heading angle of the last 5 epochs in the Adapt2 stage. The coefficient of the rMT predictor was also not significant different in this assessment of retention ($t(24) = 1.7$, $p = 0.1$).

As a point of comparison, we performed similar correlational analyses for the Sham group. Given that these participants did not receive tDCS stimulation, there is no reason to expect individual differences in rMT to be predictive of any measures of performance on the adaptation task. Indeed, the correlations were consistent with these null predictions (Fig. 5b–c): rMT and angular error were not correlated in the Adapt2 stage ($r = -0.27$, $t(12) = -0.95$, $p = 0.36$) nor in the Post2 stage, ($r = -0.04$, $t(12) = -0.52$, $p = 0.88$). It is noteworthy that the non-significant correlation is in the opposite direction of that observed for the M1-Anodal group during the Adapt2 stage. As such, it is unlikely that the dissimilar result for the two groups here is due to reduced power for the Sham group.

In the second approach we used a non-parametric permutation test to examine the association between rMT and angular error without being constrained to predefined time windows. The correlation between rMT and angular error was calculated for all 79 epochs, with a cluster analysis employed to identify windows in which angular error was associated with rMT.

In the M1-Anodal group, a cluster of significant positive correlations was evident from epoch 27 to epoch 37 ($p < 0.05$, indicated by a black horizontal bar in Fig. 6). Within the detected interval, participants with low rMT (cyan) tend to have lower angular error than participants with high rMT (pink). This advantage became manifest around the middle of the perturbation phase and lasted for 11 epochs, or 88 reaches. By the end of the perturbation phase, the high rMT participants have reached a similar asymptotic value. No clusters were identified in the washout phase, indicating that sensitivity to brain stimulation was not predictive of short-term retention from anodal tDCS over M1.

To verify that this technique does not detect spurious effects, we conducted the same analysis in the Sham group. No significant clusters were identified at any point within the experiment.

Discussion

The present findings show that with the anodal electrode positioned over M1, tDCS enhances sensorimotor learning on a visuomotor rotation task compared to sham stimulation. The advantage was manifest as faster adaptation to the rotation. Most importantly, the boost from tDCS was related to individual differences in sensitivity to transcranial stimulation.

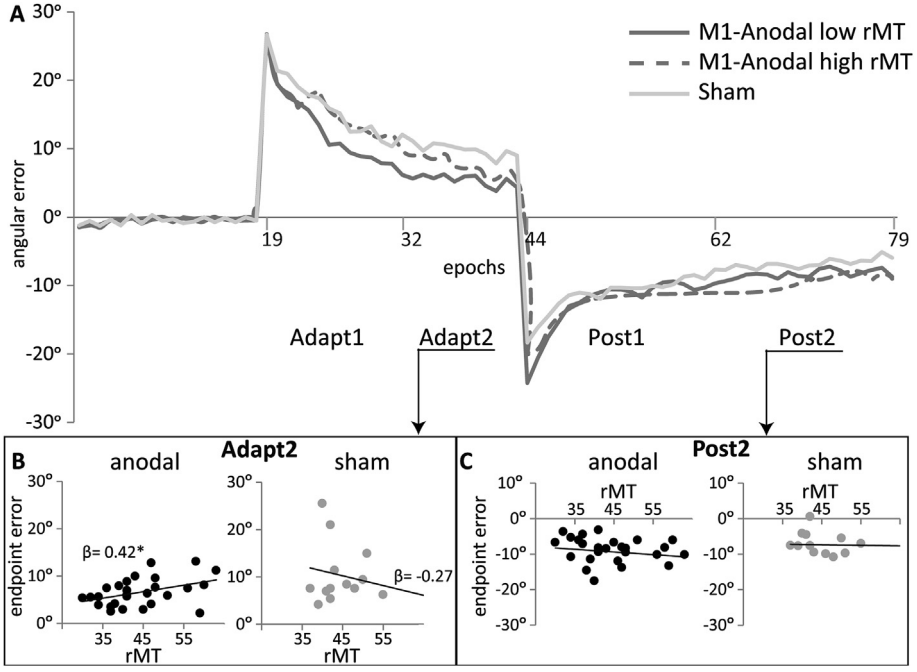

Fig. 5. Efficacy of tDCS during adaptation varies as a function of sensitivity to brain stimulation. A: For illustrative purposes, the data from Fig. 2A are replotted with the M1-Anodal group divided by a median split into those with a low rMT threshold (mean ± SD, 36 ± 3, high sensitivity) and those with a high rMT threshold (mean ± SD, 49 ± 7, low sensitivity). All statistics used continuous measures of rMT. B, C: Correlations between rMT and angular error during the second half of the perturbation phase (Adapt2) and washout phase (Post2) for the M1-Anodal and Sham groups. The gray lines show the mean (±SE) values of the Sham group. β = standardized regression slope. * = $p < 0.05$.

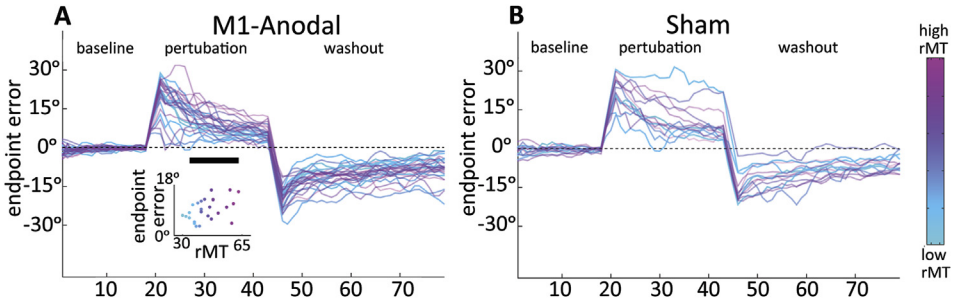

Fig. 6. Permutation test identifying epochs in which efficacy of tDCS varies as a function of sensitivity to brain stimulation. Functions for each individual in the M1-Anodal (A) and Sham (B) groups on the visuomotor adaptation task, color coded by rMT, ranging from blue (low rMT, high sensitivity) to purple (high rMT, low sensitivity). In the M1-Anodal group (A) the black horizontal line indicates consecutive epochs in which a cluster-based permutation test revealed significant correlation between rMT and performance. The insert shows the correlation between rMT and average angular error in the identified cluster. Angular error data were smoothed using a 3-epoch window to allow better visualization; all statistical analyses were conducted on unsmoothed data.

Estimating individual differences in sensitivity to non-invasive brain stimulation

Concerns regarding the reliability and robustness of tDCS-induced effects have been the subject of considerable discussion [5,6,13,27–29]. The failure to obtain robust effects from tDCS likely stems, in part, from the relatively weak currents that are induced at the cortical surface [30,31]. Moreover, the magnitude of these effects will vary across individuals given that the stimulation is applied at a fixed intensity, without consideration of variables that influence current conduction (e.g., skull thickness) or the physiological response to the current changes (e.g., neurotransmitter concentration).

To ask if these individual factors are behaviorally relevant, we examined whether differences in sensitivity to brain stimulation might account for some of the variability observed in the impact of tDCS on sensorimotor adaptation. We operationalized stimulation sensitivity as the rMT identified with TMS. A positive correlation was observed between this measure and the angular error at the end of the perturbation phase. This finding suggests that the variability in efficacy of tDCS does not only reflect random measurement error; rather, some component of the variability is systematically related to individual differences in sensitivity to brain stimulation.

Although TMS and tDCS influence cortical physiology through different mechanisms, individual differences in anatomical and physiological characteristics might influence the efficacy of both stimulation protocols in a similar manner. Practitioners of TMS typically adjust for these individual differences, setting the stimulation level to be some fixed proportion of the individual rMT. This procedure underscores the considerable variability in sensitivity to TMS: In the current data set, the TMS intensity for rMT ranged from 30% to 68% of the MSO across participants. Assuming there is some relationship between individual differences in the response to TMS and tDCS, this large range would indicate that there will be considerable variability in the efficacy of tDCS when applied at a fixed intensity for all participants.

We recognize that rMT is best viewed as a proxy and does not provide a mechanistic account for individual variation in sensitivity to brain stimulation. In addition to anatomical factors such as skull thickness and scalp-to-cortex distance [32], rMT is influenced by factors such as neurotransmitter concentration [33,34], age, stress and phase within the menstrual cycle [35]. Although our approach cannot identify the sources of variation in rMT, we assume the measure can serve as a composite index of multiple variables. Indeed, this hypothesis is supported by recent modeling work showing a relationship between rMT and tDCS-induced electric fields [36,37].

Sophisticated models have been developed to predict current flow from the conduction properties of the layers separating the electrode interface and the targeted brain region [38,39], validated in studies involving recordings of cortical electrical fields during tDCS in patients undergoing surgery for epilepsy [30,31]. These models, as currently implemented, are purely anatomical. They do not consider other variables that may influence variation across individuals in terms of the neural response to tDCS, or the manner in which electrical field models transfer into physiological effects given the microscopic features of anatomy (e.g., relative orientation of neural target). A future challenge is to see if these current flow models can be employed to identify optimization criteria based on individual MRI scans and determine if these procedures improve the efficacy of tDCS [40,41].

Similarly, an important future question is whether our approach can be used to tailor the level of tDCS stimulation. For instance, rMT from TMS could be used to adjust the tDCS stimulation level such that the effective dose is more homogenous across individuals (e.g., higher stimulation level for individuals with a high rMT). We note, though, that there are limitations with the use of such an empirical method to account for individual differences in the efficacy of tDCS. In particular, only a few cortical areas, namely M1 and primary visual cortex, offer the possibility to use TMS to obtain direct measures (MEPs, phosphenes) that could be used as proxies for sensitivity to brain stimulation. However, it may be possible to use TMS in combination with EEG to enlarge the range of cortical areas for which TMS could be used as a tool to predict tDCS effects [42].

Influence of tDCS over M1 on motor learning

To assess the behavioral consequences of tDCS, we employed a near-identical design as that employed by Galea et al. [16, see also 43]. In that study, an intriguing double dissociation was observed between tDCS targeted at M1 and the cerebellum. The former was found to enhance retention, whereas the latter was found to enhance learning [but see 44]. This dissociation was interpreted as consistent with the hypothesis that the cerebellum is essential for using error signals to recalibrate an internal model and the motor cortex for retaining a representation of that internal model.

Empirically, the current results present a more and more nuanced picture. As in the Galea study, tDCS stimulation with the anodal electrode over M1 induced a change in performance relative to sham stimulation. However, we observed enhanced learning, with the participants in the M1-Anodal group showing a greater reduction in angular error by the end of the perturbation phase [see also 45]. Adding further support to the argument that the learning benefits from M1anodal tDCS accrue during exposure to the altered environment comes from the fact that our proxy of sensitivity to

brain stimulation was correlated with performance changes during the perturbation phase, but not during the washout phase.

Nonetheless, we do not take this pattern as providing evidence favoring a learning-based over a retention-based account of M1 contributions to sensorimotor adaptation. Indeed, we think it problematic to behaviorally separate learning from retention with the current task. First, acquisition and retention are measured in a continuous manner in this task, whereas traditional tests of retention in memory studies entail some delay between the learning and recall phases.

Second, and more compelling, computational models of sensorimotor adaptation [46–49] make clear that even if a manipulation selectively affected retention, it would also be manifest during the acquisition phase. The simplest state-space model that has proven effective in characterizing performance changes includes two parameters to account for trial-to-trial changes in performance. One represents the learning rate, indicating how much of the error is corrected for across trials. The other represents the retention factor of the current state. Whereas the retention process can, in theory, be isolated in a washout phase when the error signal is removed, the same does not hold for the learning process. The retention of the memory of the most recent state should be evident at all stages of performance. More complex experimental protocols, ones that are amenable to model-based analyses, are required to provide a clearer view on how tDCS impacts sensorimotor adaptation.

Conclusions

The current results demonstrate that individual differences in sensitivity to brain stimulation can account for some of the variability observed when using tDCS to perturb brain function. Developing protocols that can account for these individual differences should improve the utility of tDCS as a method for basic research and translational applications.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.03.008.

Conflicts of interest disclosure

The authors declare no competing financial interests.

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