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Efficacy of Anodal Transcranial Direct Current Stimulation is Related to Sensitivity to Transcranial Magnetic Stimulation

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has become an important non-invasive brain stimulation tool for basic human brain physiology and cognitive neuroscience, with potential applications in cognitive and motor rehabilitation. To date, tDCS studies have employed a fixed stimulation level, without considering the impact of individual anatomy and physiology on the efficacy of the stimulation. This approach contrasts with the standard procedure for transcranial magnetic stimulation (TMS) where stimulation levels are usually tailored on an individual basis.
Objective/Hypothesis: The present study tests whether the efficacy of tDCS-induced changes in corticospinal excitability varies as a function of individual differences in sensitivity to TMS.
Methods: We performed an archival review to examine the relationship between the TMS intensity required to induce 1 mV motor-evoked potentials (MEPs) and the efficacy of (fixed-intensity) tDCS over the primary motor cortex (M1). For the latter, we examined tDCS-induced changes in corticospinal excitability, operationalized by comparing MEPs before and after anodal or cathodal tDCS. For comparison, we performed a similar analysis on data sets in which MEPs had been obtained before and after paired associative stimulation (PAS), a non-invasive brain stimulation technique in which the stimulation intensity is adjusted on an individual basis.
Results: MEPs were enhanced following anodal tDCS. This effect was larger in participants more sensitive to TMS as compared to those less sensitive to TMS, with sensitivity defined as the TMS intensity required to produce MEPs amplitudes of the size of 1 mV. While MEPs were attenuated following cathodal tDCS, the magnitude of this attenuation was not related to TMS sensitivity nor was there a relationship between TMS sensitivity and responsiveness to PAS.
Conclusion: Accounting for variation in individual sensitivity to non-invasive brain stimulation may enhance the utility of tDCS as a tool for understanding brain–behavior interactions and as a method for clinical interventions.

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Introduction

Non-invasive brain stimulation has become an important tool for basic research in human brain physiology, cognitive neuroscience and translational methods designed to provide new clinical interventions. A variety of methods have been developed for human application over the past thirty years, including transcranial magnetic stimulation (TMS), paired associative stimulation (PAS) [1] and transcranial direct current stimulation (tDCS) [2]. These methods have been used to perturb or enhance motor and cognitive function [2], probe the dynamics of cortical physiology [3], and treat

Abbreviations: ADM, abductor digiti minimi muscle; M1, primary motor cortex; MEPs, motor evoked potentials; MEP_{1mV} intensity, 1 mV peak-to-peak amplitude; MSO, maximum stimulator output; MT, motor threshold; PAS, paired associative stimulation; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

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symptoms associated with a range of neurological and psychiatric disorders [4–6].

In tDCS, a direct electrical current is used to modify neural excitability, inducing subthreshold membrane polarization shifts, whose direction depend on stimulation polarity. At rest, corticospinal excitability is assumed to increase when the anodal electrode is positioned over the primary motor cortex (M1) and decrease when the cathodal electrode is positioned over M1. Based on the membrane polarization effects, applying tDCS for a few minutes results in alteration of the strength of glutamatergic synapses, and thus long-lasting neuroplastic effects [7]. Anodal tDCS produces an increase in TMS-elicited MEPs amplitudes, whereas cathodal tDCS produces a decrease in MEPs amplitudes.

PAS offers an alternative method of plasticity induction. In this method, an electrical stimulus is applied over a peripheral nerve in combination with TMS over the contralateral motor cortex. MEPs alteration depend on the interstimulus interval (ISI) between the TMS pulse and the nerve stimulation [1,8]: MEPs decrease with a short ISI (e.g., 10 ms) due to the asynchronous activation of motor cortex neurons by the peripheral and cortical stimulus, and increase with a longer ISI (e.g., 25 ms), presumably due to synchronous activation.

As currently practiced, the intensity of stimulation in most TMS and PAS studies is established on an individual basis. That is, the desired stimulation level is established on a functional/physiological criterion rather than set to a constant level across participants. To this end, a procedure is conducted prior to the experiment proper to establish the required stimulation intensity to meet some defined criterion. The criterion could be resting motor threshold, operationalized as the intensity required to elicit MEPs of 50 μV in at least 50% of the trials [9], or a targeted size of the MEPs (e.g., 1 mV [10]). This approach is designed to minimize the impact of task-irrelevant factors that introduce inter-participant variability. For example, the physiological impact of a TMS pulse of a fixed intensity may be influenced by anatomical factors such as skull thickness and the cortical orientation of the targeted neural region [11,12]. As such, a TMS pulse of a fixed intensity will result in variable MEPs amplitudes across individuals. By tailoring the TMS intensity on an individual basis, a common baseline is established and, as a consequence, the experiment is more sensitive to the effect of an experimental manipulation.

While stimulation factors such as intensity, duration, and electrode configuration have been shown to determine efficacy of tDCS at the group level (e.g. Ref. 10), the stimulation intensity used in tDCS studies is set to a fixed level for all participants. In some studies, the intensity might be 1 mA, in others 2 mA. But unlike TMS or PAS, the intensity is fixed for all participants. The use of fixed stimulation intensity in tDCS add a source of variability that is extraneous to the experimental manipulation, and might be a factor contributing to the inter-individual variability of tDCS effects [13–16].

As a first step in exploring this issue, we examined the relationship between individual differences in sensitivity to TMS and the efficacy of tDCS. We performed an archival review, analyzing data from prior studies published by our group to explore if tDCS-induced changes in corticospinal excitability are related to individual differences in sensitivity to TMS. For all participants, the data sets included the TMS intensity required to evoke MEPs amplitudes of 1 mV elicited by single pulse TMS, operationalized as percentage of maximum stimulator output (MSO). We predicted that participants most sensitive to TMS (low MSO) will show the greatest response to tDCS and that participants who are less sensitive to TMS (high MSO) will show a smaller response to tDCS. In other words, we predict a negative relationship between MSO and tDCS effects on corticospinal excitability. As a control measure, we performed a similar analysis relating TMS sensitivity to MEP changes obtained in two PAS protocols. Given that stimulation parameters in the PAS protocol are determined individually, we did not expect to observe a relationship between MSO and PAS effects on corticospinal excitability.

Materials and methods

The analyses reported here were performed on data sets from three studies [17–19]. The focus of these studies was on the impact of pharmacological interventions on plasticity associated with tDCS and PAS. In the current study, we restricted the analysis to the control data from these studies, the conditions in which the participants were administered a placebo substance.

Participants

For the tDCS conditioning groups, data were available from 34 participants who had received anodal and cathodal tDCS, and from two additional participants who had only received anodal tDCS (n = 36, 16 women, 20 men, 27 ± 5 years old). For the PAS conditioning groups, data were available from 36 participants (n = 36: 15 women and 21 men; 27 ± 4 years old). As assessed by the Edinburgh Handedness Inventory [20], all participants were right-handed.

All participants were naive to the purpose of the study and were financially compensated. The protocol was approved by the ethics commission of the University Medical Center of the University of Gottingen and conformed to international standards for testing with human participants (Declaration of Helsinki). All participants provided written informed consent prior to the start of the experiment.

Transcranial magnetic stimulation

TMS was delivered through a 70 mm, figure-of-eight coil driven by a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was positioned over left motor cortex to elicit MEPs in the right abductor digiti minimi muscle (ADM). The coil was placed tangentially on the scalp with the handle oriented toward the back of the head and laterally at a 45° angle from the midline, an orientation that is approximately perpendicular to the central sulcus. Single-pulse TMS was applied at 0.25 Hz to identify the optimal spot for eliciting MEPs in the ADM. This hotspot was marked on the participant's scalp to provide a reference point for the experimental session.

The intensity of TMS (defined in terms of percentage of maximum stimulator output, MSO) was adjusted to elicit, on average, baseline MEPs of 1 mV peak-to-peak amplitude (MEP_{1mV} intensity). The EMG display was set to allow the experimenter to easily visualize a 1 mV change in the EMG signal. The experimenter then adjusted the output manually, seeking a stimulation level that produced MEPs of approximately 1 mV amplitude. The final value corresponded to the stimulation level in which 1 mV MEPs were assumed to be elicited in the target muscle. This was probed via baseline MEPs recording, for which 25 MEPs were obtained. If mean baseline MEPs size was within the range of 1 mV ± 20% MSO, this value was accepted. If it exceeded these limits, TMS intensity was determined again. The final stimulation level was fixed at this level for the remainder of the experiment.

EMG was recorded from surface electrodes placed over the right ADM. The EMG signal was monitored on-line to ensure that participants maintained a relaxed posture over the course of the experiment. The EMG signals were amplified (gain, 1000) and bandpass-filtered (2 Hz–2 kHz). The signals were digitized at 5kHz for off-line analysis by Signal software and CED 1401 hardware (Cambridge Electronic Design). EMG data were collected for 200 ms on each trial, starting 80 ms before the TMS pulse.

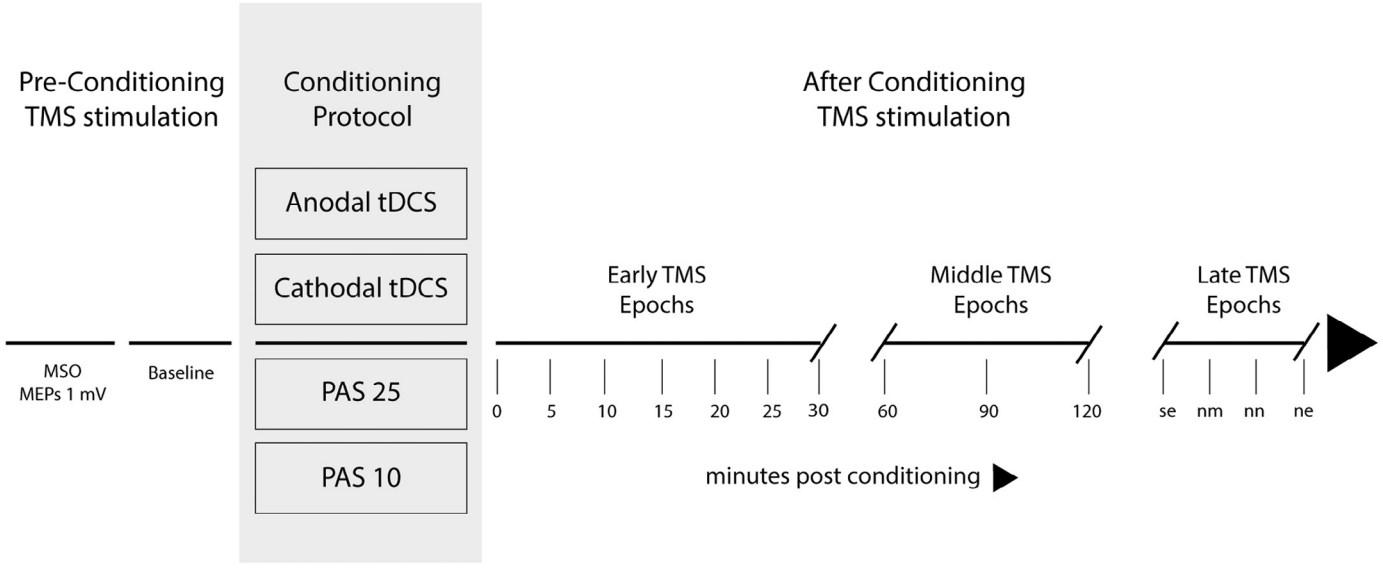

Figure 1. Experimental procedure. Data were available from studies using four different conditioning protocols: anodal tDCS, cathodal tDCS, PAS 25 stimulation, or PAS 10 stimulation. For each participant, the maximum stimulator output (MSO) was set to elicit baseline MEPs that averaged 1 mV peak-to-peak amplitude. A baseline measure of corticospinal excitability was obtained prior to conditioning protocol and then at multiple time points following conditioning. Three time windows were defined: The Early window included all epochs between 0 and 30 min and the Middle window included epochs between 60 and 120 min. A Late window was composed of epochs obtained after the initial 2-hour session: same evening (se), next morning (nm), next noon (nn), next evening (ne).

Conditioning protocols

Transcranial direct current stimulation (tDCS)

tDCS was delivered through a battery-driven constant current stimulator (Neuroconn, Germany). The current was applied through saline-soaked surface sponge electrodes (7×5 cm; area 35 cm^2). The active electrode was centered over the ADM hotspot of the left M1. The reference electrode was positioned above the contralateral supraorbital ridge. tDCS was applied with a current intensity of 1 mA for 13 minutes in the anodal tDCS condition and 9 min in the cathodal tDCS condition, with a 10-s ramp at the beginning and end of the stimulation. These stimulation protocols have been shown to induce changes in corticospinal excitability for up to 1 hour after the end of stimulation [21,22].

Paired associative stimulation (PAS)

For the PAS protocol, an electrical pulse was delivered (Digitimer D185 multipulse stimulator) to the right ulnar nerve at the wrist, paired with a TMS pulse to the left M1 ADM hotspot. The intensity of the electrical pulse was set to three times the sensory perceptual threshold. Sensory perceptual threshold was defined as the minimal electrical stimulation intensity (in Volts), which resulted in a somatosensory perception. Somatosensory threshold was identified by stepwise increase of the stimulation intensity. TMS intensity was adjusted to result in a mean MEPs amplitude of 1 mV [1,23]. The electrical and magnetic pulses were separated by an interval of either 10 or 25 ms, with the peripheral nerve pulse always followed by the TMS stimulus. These paired pulses were administered once every 20 s for 30 min. The ISI determines the direction of induced plasticity. With the 10 ms ISI (PAS10) excitability is attenuated whereas with the 25 ms ISI (PAS25) excitability is enhanced [1,23,24]. Note that, unlike tDCS, the parameter settings for PAS are identified on an individual basis.

Procedure

Participants sat in a comfortable chair with both hands resting on a pillow, palms down, with the arms in a semi-flexed position. The experimental protocol is summarized in Fig. 1. After establishing the TMS intensity required to produce MEPs of 1 mV, an initial set of 25 baseline MEPs was obtained (0.25 Hz). Participants were then exposed to one of the four conditioning protocols. Participants were blind concerning the tDCS polarity condition (anodal or cathodal) or PAS timing (PAS10 or PAS25). Immediately after conditioning, a second set of 25 MEPs was obtained with TMS. This procedure was repeated every 5 minutes for the first 30 minutes post-conditioning, and then every 30 min for the next one and a half hours. The participants returned for an additional block of TMS trials that evening, and three times during the next day (morning, noon, and evening). In sum, motor cortex excitability was probed in 14 epochs after tDCS or PAS conditioning.

For participants who completed more than one conditioning protocol, a minimum of seven days separated successive protocols. For these participants, the intensity of TMS stimulation was adjusted at the beginning of each session and the order of conditioning type was randomized.

Data analysis

The goal of this study was to determine if individual differences in the efficacy of tDCS can, in part, be explained by individual differences in sensitivity to TMS. We looked at this question using a median split procedure in which we divided the participants within each conditioning protocol into two groups, Low and High TMS Intensity. The Low Intensity group was composed of individuals requiring lower TMS stimulation levels (MSO) to produce 1 mV MEPs at baseline; the High Intensity group was composed of

individuals requiring higher TMS stimulation level to produce 1 mV MEPs.

The data were visually inspected to exclude trials in which there was significant background EMG activity greater than 0.01 mV in the 200 ms window preceding the TMS pulse [25,26]. We also removed MEPs outliers, defined by those in which the amplitude was ±2 sd of the mean MEPs (for each condition).

MEPs were averaged within each of the 14 epochs. We first evaluated the normality of the data for each epoch with the Kolmogorov–Smirnov test (using the residuals of the raw data). The average MEP values for each epoch were then normalized with respect to baseline on an individual basis, with values greater than 1 indicating an increase in excitability, and values smaller than 1 an excitability reduction. For epochs in which the data were normally distributed, we used a series of t-tests to examine if a conditioning protocol produced a significant change in MEPs amplitude, relative to baseline.

The data were pooled to create three time windows: Early (0–30 min), Middle (60–120 min), and Late (evening and next day). Given that MEPs in all four protocols had returned to baseline in the Late window, we restricted this analysis to the Early and Middle windows. Separate ANOVAs were conducted for each conditioning protocol, with one between-subject factor (Group: Low Intensity vs. High Intensity) and a within-subject repeating factor (Time: Early vs. Middle epoch). Given that there were some violations of normality, we supplemented the ANOVA with nonparametric permutation statistics (see Results section).

Correlation coefficients were calculated for the two tDCS protocols, with one variable being the TMS stimulation level and the other being the average normalized MEP value for the Early epoch. With this analysis, variation in TMS intensity was treated as a continuous variable rather than being categorically divided into Low and High Intensity groups.

Results

Individual differences in TMS intensity

Participants were divided into two groups based on the stimulation level required to produce 1 mV MEPs. The median MSO was similar for all four conditioning protocols. For each protocol, participants with values lower than the median MSO were assigned to the Low Intensity group and participants with values higher than the median MSO were assigned to the High Intensity group. For anodal tDCS, the median MSO was 49.0 (Low: n = 17, MSO range: 30–48; High: n = 19, MSO range: 49–69). For cathodal tDCS the median MSO was 47.5 (Low: n = 17, range: 32–47; High: n = 17, range: 48–68). For PAS25, the median MSO was 48.5 (Low: n = 18, range: 31–48; High: n = 18, range: 49–67). For PAS10, the median MSO was 47.5 (Low: n = 18, 34–47; High: n = 18, range: 47–67).

Efficacy of the conditioning protocols

As assessed by Kolmogorov–Smirnov test, the MEPs data in the Anodal condition met the criteria for normality in 13 of the 14 epochs, with the one violation at 15 min. However, more frequent violations of normality were observed in the other three conditioning protocols. The cathodal data were not normally distributed for four epochs (t25, t90, t120, next day noon). For the PAS protocol, violations were observed in four epochs for the PAS10 condition (15 min, 20 min, 25 min, same evening) and six epochs in the PAS25 condition (5 min, 10 min, 15 min, 20, 120 min, next evening). Given this mixed picture, we present both parametric and non-parametric statistics in our evaluation of the effects of the conditioning protocols.

Consistent with previous reports, all conditioning protocols led to measureable changes in corticospinal excitability (Fig. 2). Relative to baseline, anodal stimulation and PAS25 produced an increase in MEPs, whereas cathodal stimulation and PAS10 decreased MEPs. The change from baseline was significant (all <0.05, analysis restricted to epochs that did not violate test of normality) for all four conditioning protocols for up to 90 min after conditioning. At 120 min, the MEPs were indistinguishable from baseline for tDCS, while remained significant for PAS. No persistent changes were observed on the evening following conditioning, or on the subsequent day.

Modulation of conditioning effects due to individual differences in TMS intensity

To examine if variation in sensitivity to TMS influenced the efficacy of the conditioning protocols, we compared the dynamics of the MEPs changes for participants in the Low and High Intensity

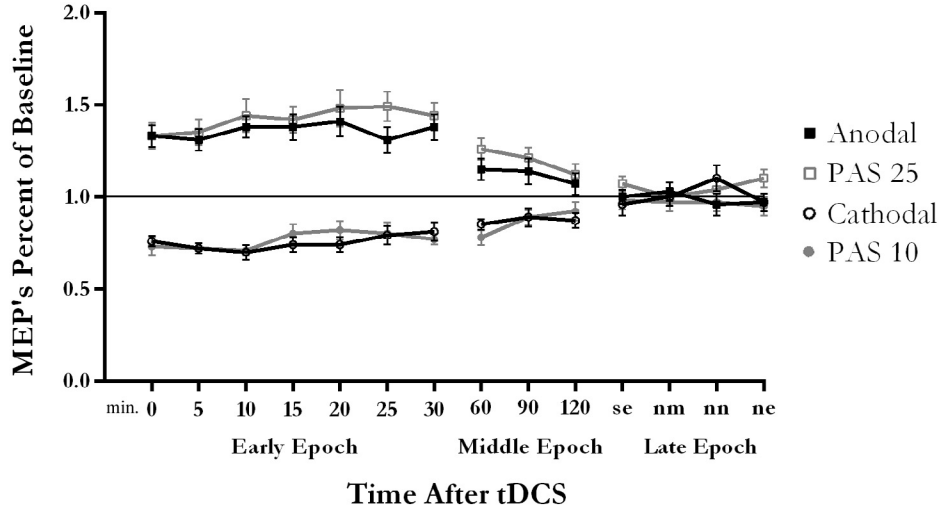

Figure 2. MEPs changes at each epoch for the four conditioning protocols. The data are averaged over all participants for a given condition. In black are shown MEPs changes after tDCS conditioning protocols (anodal filled square, cathodal empty circle) and in gray are shown MEPs changes after PAS conditioning protocols (PAS 25 empty square, PAS 10 full circle). Error bars indicate SEMs.

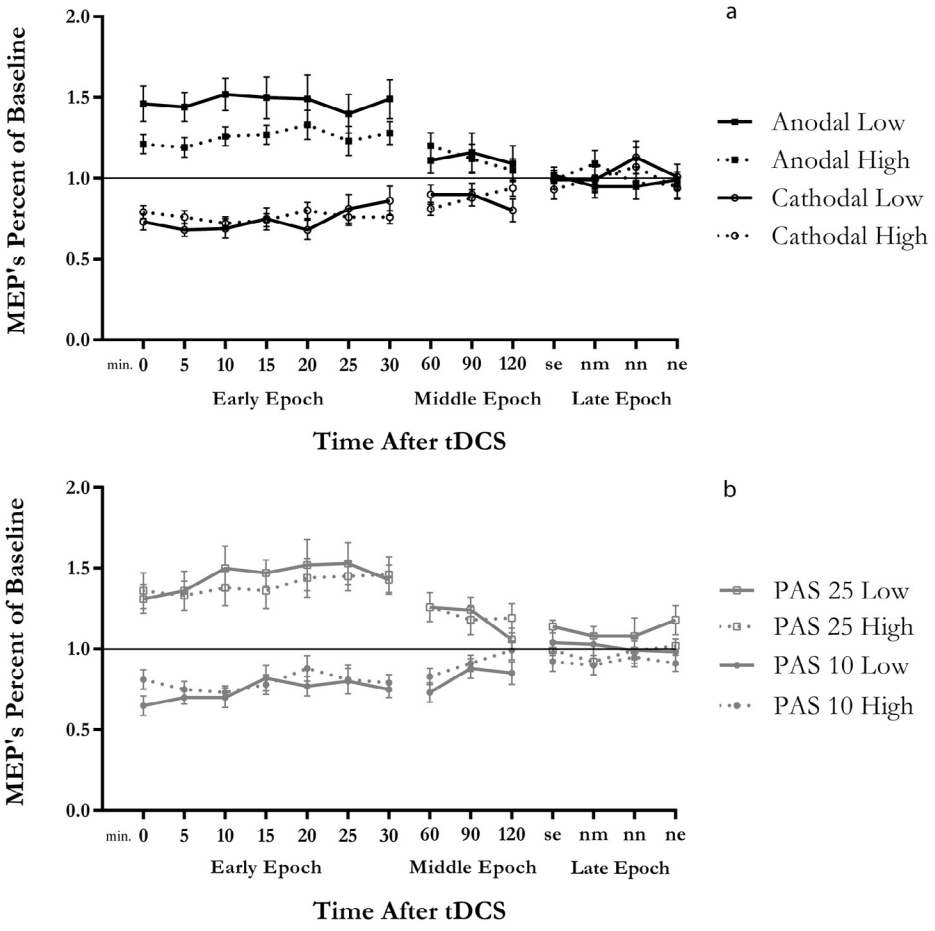

Figure 3. MEPs changes at each epoch for the tDCS (a) and PAS (b) conditioning protocols, with the participants in each condition divided into Low Intensity (filled lines) and High Intensity groups (dotted lines). The division was based on a median split defined by the level of TMS stimulation required to elicit 1 mV MEPs prior to the conditioning protocol. Error bars indicate SEMs.

groups. The effects of conditioning remain relatively constant for the first 30 min and then decrease over the remaining epochs in the initial 2-hour session (Fig. 3). Given this, we pooled the MEPs data into two time periods, Early (0–30 min) and Middle (60–120 min), excluding the other epochs since there was no residual effect of the conditioning protocols. For anodal stimulation, the main effect of Time, $F(1,34) = 20.69$, $p < 0.001$, but not of Group, $F(1,34) = 1.59$, $p = 0.216$, was significant. However, the interaction of these two factors was significant, $F(1,34) = 4.44$, $p = 0.043$. As can be seen in Figs. 3a and 4, anodal tDCS produced a larger increase in MEPs in the Low Intensity group, but this effect was limited to the early time window (Early: $t = 2.08$, $p = 0.045$; Middle: $t = -0.32$, $p = 0.98$). This result is consistent with the hypothesis that individual differences in sensitivity to TMS impact the efficacy of anodal tDCS. Contrary to our expectations, this pattern was not observed with cathodal tDCS. Here we observed a main effect of Time, ($F(1,32) = 11.241$, $p = 0.002$), but no effect of group ($F(1,32) < 1.0$) nor an interaction ($F(1,32) < 1.0$).

Individual differences in TMS intensity did not influence the efficacy of PAS (Fig. 3b). For both PAS10 and PAS25, there was a significant effect of Time (all p's < 0.03), but not of Group and the respective interactions (all p's > 0.20). The null effects here are in line with expectations given that, for the PAS protocols, TMS intensity has been adjusted individually.

The violations of normality in some of the epochs are unlikely to have had a major impact on the ANOVAs. First, we pooled the data across epochs to obtain more robust samples for each individual. Second, violations of normality increase the likelihood of a false positive result, although simulation studies have shown that this increase is modest for moderate deviations from normality [27–29]. We did not obtain significant Group or interaction effects for the three

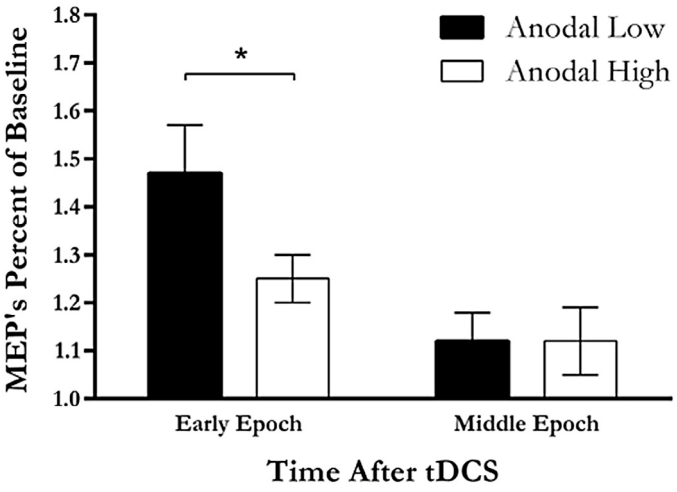

Figure 4. MEPs changes in the Early and Middle time windows for participants in the anodal tDCS protocol, with the participants divided into Low Intensity (black filling) and High Intensity (white filling) groups. Error bars indicate SEMs.

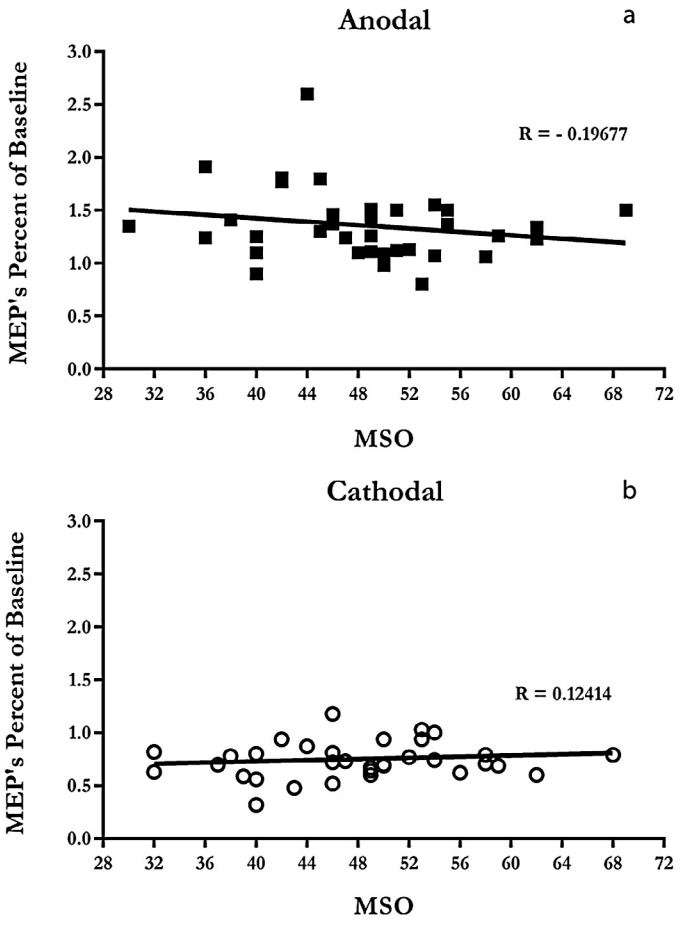

Figure 5. Correlation between intensity of TMS stimulation and averaged normalized MEP value. Data are from the Early time window (0–30 min after intervention) for the anodal (a) and cathodal (b) tDCS groups.

conditioning protocols in which there were substantial violations. Third, the normality criterion was generally met for the anodal group, the one protocol showing the Group × Time interaction. However, given the violations of the normality assumption, we also applied nonparametric permutation statistics to assess the MEPs data, comparing the Low and High Intensity groups in the Early and Middle time windows for the different conditioning protocols. Randomization tests were conducted in which individuals were randomly assigned, with replacement, to one of two groups to create a distribution of the expected differences (10,000 permutations). From this distribution, we calculated the p value for our observed values. Consistent with the parametric analyses, the difference between the Low and High Intensity groups for the anodal group was significant in the Early epoch ($p = 0.021$). There was no effect of group for the other conditioning protocols in the early window, nor an effect of group for any of the conditioning protocols in the Middle epoch (all p's > 0.35).

We also explored the data in a continuous manner, correlating stimulation intensity with the post-conditioning change in MEPs (Fig. 5). In the Early epoch there was a negative correlation for the anodal group ($r = –0.197$, $p = 0.125$) and a positive correlation for the cathodal group ($r = 0.124$, $p = 0.241$). Although neither correlation was significant, both are in the predicted direction if the efficacy of tDCS conditioning is related to the TMS stimulation level. We note that one participant had a much larger MEP (MSO 44/MEP 2.60) than the group, and another a much larger MSO (MSO 69/MEP 1.50), raising concerns that these correlations might be driven by outliers. However, the correlations remain unaffected when redone without these individuals. Dropping the large MEP participant reduced the correlation to –0.18; dropping the large MSO participant increased the correlation to –0.25. Given that neither value was more than 2.5 SD from the average, we have opted to include all of the data.

Discussion

The data presented in this archival analysis demonstrate that the efficacy of tDCS in inducing changes in corticospinal excitability varies as a function of individual differences in the sensitivity to TMS. Individuals requiring a lower TMS stimulation level to produce a criterion MEP amplitude size showed a larger change in MEPs following anodal tDCS, compared to individuals requiring a higher TMS stimulation intensity. This effect was not found for cathodal tDCS. Given the widespread use of anodal tDCS to modulate motor and cognitive functions, these results highlight a potentially relevant covariate to consider when evaluating the efficacy tDCS. It should be taken into account that the TMS intensities used in this analysis to define low and high intensity groups should not be taken as absolute values given the variation in output delivered by the TMS device from different manufacturers.

Individual sensitivity to TMS is widely recognized as a critical factor in the TMS literature [30]: indeed the standard protocol in the field entails the use of a pre-experiment phase to "equate" the physiological/functional stimulation level across individuals. This procedure, regardless of whether the criterion involves establishing resting threshold or a target MEP size, always reveals substantial variation. For example, the stimulation level required to produce a 1 mV MEP varied from 30% to 69% of the maximum output of the stimulator in the current data set. Although TMS and tDCS operate under different mechanisms to influence cortical physiology, anatomical and physiological properties that influence the efficacy of stimulation might be similar within an individual. Relevant factors would include skull thickness, overall brain shape, the pattern of cortical folding, receptor distribution, transmitter and neuromodulator availability.

Methodologically, researchers have not considered individual variation in sensitivity to brain stimulation as a means to adapt stimulation protocols for tDCS studies. Rather, the convention has been to employ a fixed conditioning protocol for all individuals. The results presented here suggest that using a fixed stimulation level may negatively impact the robustness of tDCS research given that one source of variability, individual sensitivity to tDCS, is not controlled. The importance of this issue is evident in recent discussions on the efficacy and reliability of tDCS [13–16,31]. We suggest that some of this variability may arise from the failure to consider individual differences in the sensitivity to tDCS.

The relationship between sensitivity to TMS and the efficacy of tDCS appears to be modest. While the group effect is substantial in our median split analysis, when the data were treated in a continuous manner, the correlation between our two measures was only –0.20. By conventional estimates, this would mean that differences in sensitivity account for only 4% of the variance. We note that this estimate represents the lower limit given that correlations are limited by the reliability in the measurement of each variable; one can assume that reliability is lower at the individual level compared to the group analysis. Nonetheless, there are many reasons to expect limitations in the relationship between TMS and tDCS. While individual variation in anatomy or neurotransmitter concentrations should have similar effects on TMS and tDCS, other variables such as hair thickness and skin conductivity impact the efficacy of tDCS, but not TMS.

Factors underlying individual differences in the efficacy of tDCS have been considered in some studies. Opitz et al. [32] used a model of the head to investigate how anatomical features shape the electric field distribution in the brain during tDCS. They showed that individual characteristics, such as the thicknesses of the skull and sulcal depth, influence electrical field distribution. Taking a similar approach, Kim et al. [33] showed that a composite of anatomical features based on individual MRIs was related to behavioral changes in working memory.

To date, only a few studies have directly examined individual responsiveness to TMS and anodal tDCS [34]. López-Alonso et al. [35] used a cluster analysis to test whether baseline TMS measures (e.g., resting motor threshold and stimulation level required to produce 1 mV MEPs) were correlated with the efficacy of tDCS in modulating corticospinal excitability. This analysis failed to reveal a relationship between responsiveness to the TMS and tDCS measures. This result stands in contrast to our findings. However, the authors do not report the range of stimulation levels employed in the study, making it difficult to compare with our study. In addition, a large percentage of the participants (45%) failed to show enhanced MEPs following anodal tDCS (non-responders group) while in our pool of subjects only 3 subjects out of 38 were non-responders (8%).

We also note that baseline MEPs amplitudes differed between clusters in the López-Alonso et al. [35] study. The non-responders group had significantly higher MEPs compared to the responders group. One possibility is that the lower baseline MEPs in the responders may have afforded greater sensitivity to observe an increase in excitability after tDCS, a hypothesis consistent with the findings of Wiethoff et al. [14]. This factor is unlikely to influence our results given that baseline MEPs were similar across all groups. For example, in our median split, baseline MEPs amplitudes were close to the targeted 1.0 mV level and did not differ between the High and Low Intensity groups (mean ± SD, Low Intensity group: 1.07 ± 0.10; High Intensity group: 1.05 ± 0.14; $t = 0.35$, $p = 0.72$).

We did not observe a relationship between sensitivity to TMS and the efficacy of cathodal tDCS. Although cathodal tDCS reduced corticospinal excitability for an extended period of time, the effect was comparable for the Low and High Intensity groups. At present, we can only speculate about why the relationship observed with anodal tDCS was not observed with cathodal tDCS. It may be that the range of responsiveness to cathodal tDCS is more restricted than that of anodal tDCS. Alternatively, our results might have been influenced by the fact that the impact of cathodal tDCS on neuroplasticity is non-linear and that there is no attenuation of excitability following cathodal tDCS if the stimulation level is too strong or too weak [7,34]. Our fixed tDCS conditioning intensity of 1 mA may have been functional ineffective for participants who were least or most sensitive to TMS. Future studies that systematically vary stimulation intensity will be required to assess these hypotheses.

We also did not observe differences in our two groups in terms of the efficacy of the PAS conditioning protocols. This null result was predicted given that with PAS, the stimulation level is individually adjusted for both TMS and electrical stimulation [10]. However, Müller-Dahlhaus et al. [36] reported that resting motor threshold and stimulation levels based on a 1 mV criterion are negatively correlated with PAS20 + 2, another PAS protocol thought to produce an increase of corticospinal excitability. It is difficult to relate these results to our findings given that the PAS20 + 2 protocol in the Müller-Dahlhaus study produced inconsistent changes in corticospinal excitability. About half of their participants (52%) showed an increase in MEPs amplitude following PAS20 + 2, with the rest showing no change or a decrease in excitability. In our study, 31 of the 36 participants (86%) showed an increase in excitability with the PAS25 protocol.

In summary, our results demonstrate a relationship between individual differences in sensitivity to TMS and the efficacy of anodal tDCS. The nature of this relationship remains to be explored in greater detail: it may or may not be linear, and there remains the puzzle of understanding why the effect was limited to anodal tDCS. Moreover in the current study, the stimulation intensity for TMS was set to produce MEPs of 1 mV. We opted to use this measure since our archival data sets had a large number of participants who had received tDCS or PAS with this TMS criterion. Future studies need to investigate how the relationship between TMS sensitivity and tDCS efficacy holds for different measures of TMS sensitivity (e.g., resting motor threshold). More generally, it will be important to establish if individual differences in TMS sensitivity remain stable across the recruitment curve. Future studies will also need to address how the individual characteristics influence the efficacy of tDCS in multiple sessions, given that this has been reported to be the an efficient way to induce robust changes in healthy controls [37] and in patients [38,39]. It will also be important to consider if individual variation in sensitivity assessed over the motor cortex is relevant when considering the efficacy of tDCS targeted at other brain regions. Another approach to consider would be to obtain MEPs during tDCS, placing the TMS coil over the M1 electrode [40]. Indeed, as seen in Fig. 3, the difference between the Low and High groups is evident at our first sample, obtained just after the end of the tDCS stimulation phase. Using TMS during tDCS would allow us to see the emergence of this difference.

Of practical relevance, our results suggest an interesting direction for research designed to improve the efficacy of tDCS. Similar to standard practices in TMS research, practitioners of tDCS should consider methods to “equate”, physiologically and functionally, the stimulation level for tDCS. Given that tDCS does not produce an overt physiological response (e.g., MEPs), we propose that the stimulation level for tDCS could be adjusted on an individual basis by extrapolating from individual variation in sensitivity to TMS.

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