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Variability in Response to Transcranial Direct Current Stimulation of the Motor Cortex

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ABSTRACT

Background: Responses to a number of different plasticity-inducing brain stimulation protocols are highly variable. However there is little data available on the variability of response to transcranial direct current stimulation (TDCS).
Objective: We tested the effects of TDCS over the motor cortex on corticospinal excitability. We also examined whether an individual's response could be predicted from measurements of onset latency of motor evoked potential (MEP) following stimulation with different orientations of monophasic transcranial magnetic stimulation (TMS).
Methods: Fifty-three healthy subjects participated in a crossover-design. Baseline latency measurements with different coil orientations and MEPs were recorded from the first dorsal interosseous muscle prior to the application of 10 min of 2 mA TDCS (0.057 mA/cm^2). Thirty MEPs were measured every 5 min for up to half an hour after the intervention to assess after-effects on corticospinal excitability.
Results: Anodal TDCS at 2 mA facilitated MEPs whereas there was no significant effect of 2 mA cathodal TDCS. A two-step cluster analysis suggested that approximately 50% individuals had only a minor, or no response to TDCS whereas the remainder had a facilitatory effect to both forms of stimulation. There was a significant correlation between the latency difference of MEPs (anterior–posterior stimulation minus latero-medial stimulation) and the response to anodal, but not cathodal TDCS.
Conclusions: The large variability in response to these TDCS protocols is in line with similar studies using other forms of non-invasive brain stimulation. The effects highlight the need to develop more robust protocols, and understand the individual factors that determine responsiveness.

Introduction

Transcranial direct current stimulation (TDCS) is a widely-used tool in which a small constant direct current (usually 1–2 mA) (0.029–0.057 mA/cm^2) is applied through large pad electrodes placed on the scalp (see overview in Ref. [1]). It is thought that this changes the excitability of neurons in the brain by hyperpolarizing or depolarizing their membrane potential [2,3]. Experiments in the 1960's on cat and rat cortex showed that direct polarization for periods of several minutes produced long lasting changes in neural firing rates for several hours afterwards [4–6]. These were thought to involve synaptic plasticity since the effects were abolished by inhibitors of protein synthesis.

Similar lasting effects of TDCS in humans have been described in the motor cortex: Nitsche and Paulus found that anodal TDCS (i.e. with the anode over motor areas) increased excitability of corticospinal output, as tested using single pulse transcranial magnetic stimulation (TMS), whereas cathodal stimulation had the opposite effect [7]. Subsequent studies suggested that the effects depended on synaptic plasticity since they were abolished by pretreatment with drugs that interfered with NMDA receptor function [2,3]. However, despite the ever increasing number of studies using TDCS in fields from cognitive neuroscience to rehabilitation, there are few studies of the variability of the effects that are produced [8]. The

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latter is particularly important if TDCS is to be used therapeutically since any successful treatment should have repeatable effects on a high proportion of treated individuals.

Given the existence of interindividual differences in response to other plasticity protocols such as paired associative stimulation (PAS) and theta-burst stimulation (TBS) in which 30–50% participants fail to respond in the "canonical" way [9–17], we decided to perform a pragmatic exploratory study of variation in response to TDCS. We chose one variety of TDCS protocol (2 mA with electrode size 35 cm^2; 0.057 mA/cm^2) [18] for 10 min over motor cortex) [19] and tested the after-effects on corticospinal excitability in the standard way in relaxed healthy individuals. The selection of 2 mA (0.057 mA/cm^2) was determined by the fact that it is now becoming standard in an increasing number of behavioral, cognitive, and clinical studies due to an implicit assumption that higher intensities will enhance efficacy of stimulation [18,20]. There are no detailed studies comparing different durations of TDCS at 2 mA (0.057 mA/cm^2), although 10 min has previously been shown to have robust after-effects [19]. Participants were similar to those used in some previous papers (student volunteers) and were selected according to usual criteria. In essence we tried to create a fairly "typical" dataset to maximize the likelihood that the results would be applicable to other experimental situations.

We are aware that the results of this particular study may not apply to all varieties of TDCS, or to studies with more stringent participant inclusion criteria. However, the large variance in the response we observed suggests that it may be important to test whether other TDCS protocols are similarly affected. In the face of such variation we were also interested in whether it might be possible to predict how well a person might respond to TDCS. A number of determinants have been identified [17], and previously we had found that the response to TBS protocols was well predicted by the latency difference between MEPs evoked by single TMS pulses of different orientations [10]. It is likely that these latency differences are surrogate measures of interneuron network recruitment within the primary motor cortex [10,21]. Evidence also suggests that TDCS distinctively modulates different interneuron networks in a polarity specific manner [22,23]. We therefore examined whether latency difference measured by TMS with different orientations correlates with the responses to TDCS.

Materials and methods

Subjects

Fifty-three right-handed subjects (33 females, 20 males; 18–52 years old, mean age ± SD: 26.83 ± 8.97) participated in the study. None of the participants displayed any contraindications to TMS or TDCS, took any medication on a regular basis or had a positive history of psychiatric or neurologic diseases [24]. All participants gave written consent. The study was approved by the Ethics Committee of the University College London.

Recordings

During the experiment subjects were seated on a comfortable chair. The right first dorsal interosseous (FDI) muscle activity was recorded via Ag/AgCl cup electrodes in a belly-tendon montage. Raw signals were amplified and a bandpass filter (20 Hz to 3 kHz (Digitimer, Welwyn Garden City, UK)) was applied. Signals were digitized at 5 kHz (CED Power 1401; Cambridge Electronic Design, Cambridge, United Kingdom) and data were stored on a computer for offline analysis (Signal Version 4.08, Cambridge Electronic Design, UK was used).

Transcranial magnetic stimulation

Single-pulse TMS was performed using Magstim 200^2 stimulator (The Magstim Co. Ltd) with a connected figure-of-eight coil with internal wing diameter of 7 cm. The hotspot was identified as the position where most stable motor evoked potentials (MEPs) were elicited with the coil held 45° to the midline, tangentially to the scull and the handle pointing backwards (conventional way with current flowing posterior-anterior (PA)). The spot was consecutively marked on the scalp with a waterproof pen alongside to 2 additional orientation marks needed for exact repositioning of the coil. Resting motor threshold with PA directed current (RMTpa) was appointed as minimum stimulator output intensity needed to achieve a minimum MEP-amplitude of 50 μV in the completely relaxed FDI-muscle in at least 5 out of 10 trials. As discussed previously that latency of MEPs with different coil orientation is a surrogate measure of the relative ease of recruiting indirect wave (I-wave) input to corticospinal neurons [10,21], we employed three different coil orientations: 1) PA as described above, 2) anterior-posterior (AP) directed orientation defined by placement of the coil 180° to PA-position, and 3) latero-medial (LM) position with the coil pointing leftwards, 90° from midsagittal line. For all three orientations we assessed active motor threshold (AMT) as the lowest stimulator output intensity evoking an MEP of at least 200 μV in 5 out of 10 consecutive trials while subjects maintained 10% of their maximum voluntary contraction (MVC) in the target muscle (AMTpa, AMTap, and AMTlm).

Transcranial direct current stimulation

Transcranial direct current (TDCS) was applied to the motor cortex using a commercially available DC-stimulator from Eldith-Electro-Diagnostic & Therapeutic Systems GmbH, Germany, distributed by Magstim Co., Whitland, Dyfed, UK. One electrode was placed over the right orbit, the other electrode's center was positioned over the previously marked hot-spot. We used saline-soaked surface sponge electrodes (35 cm^2) to deliver a 2 mA (0.057 mA/cm^2) current intensity over a period of 10 min while monitoring the subject's FDI muscle activity keeping the hand in an absolutely relaxed position. Current was ramped up and down to 2 mA during the first 10 s of each session.

Experimental parameters

As described previously [10], we measured onset latency of MEPs for each orientation; 20 MEPs for PA and AP current and 10 MEPs for LM current were recorded during active condition (10% MVC in FDI). Stimulus intensities were 110% of AMTpa and AMTap for PA and AP currents and 150% AMTlm for LM current (or 50% of maximum stimulator output (MSO) in subjects whose 150% AMTlm did not reach 50% MSO). Relatively high stimulus intensities for LM currents were used in order to ensure that a D-wave was evoked [10,25]. To avoid fatigue, a short break from active contraction was taken after every 10 trials. These MEP measurements for all three directions were taken within 10–15 min. The onset latency of each coil direction was measured by an automated method described previously [10]. In brief, the onset latency of MEPs in each trial was defined as the time point where rectified EMG signals exceed an average plus two standard deviations of the pre-stimulus EMG level (−100 to 0 ms of TMS). These onset latencies were averaged and then latency differences (PA and LM, or AP and LM latency difference; PA-LM, and AP-LM, respectively) were calculated [10]. It has been shown that these latency differences are likely to be a measure of I-wave recruitment [10].

As a measure of motor cortical excitability, thirty MEPs elicited by single pulse TMS with intensity adjusted to evoke about 1 mV peak-to-peak amplitude (SI_{1mV}) at rest were recorded. Stimulation intensity was kept constant throughout the experiment. Intertrial interval was set at 4.5–5.5 s.

Study design

Subjects were enrolled in the experiment with two randomized ordered sessions (anodal vs. cathodal) each at least 3 days apart. In each experimental session, the motor hotspot was firstly determined at the intensity eliciting MEP sizes about 0.5–1 mV followed by measurements of motor thresholds (RMTpa, AMTpa, AMTap, and AMTlm). We next measured the onset latency of each coil orientation (PA, AP, and LM). During latency measurements, a short break from active contraction was taken after every 10 trials. After latency measurements followed by a 10 min break [10], as a measure of baseline motor cortical excitability, 30 MEPs with PA directed current at SI_{1mV} during rest were recorded. Stimulation intensity was kept constant throughout the rest of the experiment. After application of either anodal or cathodal TDCS for 10 min, 30 MEPs with PA current at SI_{1mV} were recorded every 5 min for 30 min (7 time points, T0, T5,… , T30). Muscle activity was monitored during experiments and trials with relevant precontraction (defined as EMG signal amplitude before TMS stimulus for 100 ms $\geq$ 0.05 mV) were discarded from offline-analysis. Importantly, the outcomes of TDCS were completely blinded until the end of experiments from all 53 subjects to the examiner (M.H.) who analyzed the latency of MEPs with different coil orientations.

Statistical analysis

We used Kolmogorov–Smirnov Test to check for normal distribution of the measurements in our dataset and applied log-transformation wherever necessary. One-way repeated measures of analysis of variance (ANOVA) was applied with the factor TIME (baseline, T0–T30) using non-normalized MEP-values. The Greenhouse–Geisser correction was used if necessary to correct non-sphericity. To test the correlation between TDCS effects and all measured variables, the responses of anodal or cathodal TDCS were firstly assessed by the grand average (GA) of normalized MEP values measured at time points T0–T30. A regression analysis was computed with the GA and all of the neurophysiological measurements values and Pearson's correlation coefficient was calculated. We also performed unpaired *t*-tests (two-tailed) to evaluate the effects of gender and time of the day. The timing of a session was defined as "am" if it was finished by 12.30 pm, all others sessions are accounted for as "pm." For these correlation analyses, significant level was set at 0.00132 according to Bonferroni's corrections since we compared 19 factors with 2 conditions. Otherwise, $P < 0.05$ was considered significant. Subjects were clustered in groups according to their individual GA in response to anodal and cathodal TDCS-condition (>1, facilitation; <1, inhibition) and a frequency spectrum was calculated. We also performed a two-step cluster analysis using log-transformed data of normalized MEP amplitude from T0 to T30 (7 levels) in order to test whether there was any tendency for subpopulations of individuals to react to TDCS in a common way. In this case, the time course of each cluster was evaluated with one-way ANOVA with non-normalized MEP sizes. For baseline measurements data are reported as mean value ± standard error of the mean (SEM). Data were analyzed using SPSS-software (SPSS ver. 19.0 for Windows; SPSS Inc.).

Results

All subjects reported light tingling over the electrode positions which completely vanished within several seconds up to 5 min.

Table 1
Baseline physiological measures (mean ± SEM, range).

	Anodal	Cathodal
RMTpa (%)	38.5 ± 1.0 (23–68)	38.6 ± 1.0 (27–72)
AMTpa (%)	29.9 ± 0.9 (17–58)	29.6 ± 0.8 (18–58)
AMTap (%)	40.2 ± 1.2 (24–78)	37.1 ± 1.4 (25–89)
AMTlm (%)	36.3 ± 1.1 (20–60)	38.5 ± 0.9 (21–87)
SI_{1mV} (%)	50.1 ± 1.5 (33–95)	55.4 ± 1.9 (33–95)
LM latency (ms)	19.1 ± 0.2 (16.5–25.3)	19.2 ± 0.2 (16.1–24.7)
PA latency (ms)	20.9 ± 0.2 (18.4–26.6)	21.0 ± 0.2 (18.5–26.3)
AP latency (ms)	22.3 ± 0.3 (18.8–29.5)	22.5 ± 0.2 (19.0–29.6)
Baseline MEP sizes (mV)	1.10 ± 0.04 (0.45–2.12)	1.14 ± 0.05 (0.26–1.60)

RMT, resting motor threshold; AMT, active motor threshold; pa, posterior-to-anterior; ap, anterior-to-posterior; lm, lateral-to-medial; SI_{1mV}, stimulus intensity to elicit MEP sizes about 1 mV.

Two subjects developed tension headache after TDCS which persisted throughout the day of the experiment after both sessions (anodal and cathodal).

Baseline physiological measurements are shown in Table 1 and were not significantly different between stimulation conditions. Figure 1A and B plot the raw MEP data from all subjects for anodal and cathodal stimulation. There was a large variation in response between individuals. One way ANOVA showed that on average there was a main effect of "TIME" in the anodal group ($F = 5.8$; df 7, 364; $P < 0.001$), whereas there was no effect in the cathodal group ($F = 1.87$, Greenhouse–Geisser corrected df = 4.8, 248; $P = 0.1$). Thus on average there was an excitatory effect of 2 mA anodal TDCS but not of cathodal TDCS. When the amplitude of the post-TDCS MEPs were normalized to baseline, one way ANOVAs showed that there was no overall effect of time over the 30 min post-TDCS assessment for either anodal or cathodal stimulation. In view of this we calculated the average effect of TDCS expressed as a mean of all the post-TDCS measures relative to baseline. Following anodal stimulation there was an increase of 1.38 (SD = 0.53; 95% confidence interval 1.23–1.52); cathodal stimulation increased the response by 1.18 (SD = 0.43; 95% confidence intervals 1.06–1.30).

Figure 1C provides a simple summary of the response profile in this population in terms of whether the mean effect post-TDCS was greater or less than 1. Just over one third of participants increased their response after anodal TDCS and decreased it after cathodal stimulation. A similar proportion increased after *both* anodal and cathodal stimulation. Thus approximately three quarters of people had an overall facilitation after 2 mA TDCS.

We also used cluster analysis to test whether there was any tendency for subpopulations of individuals to react to TDCS in a common way. Figure 2 shows that two main clusters could be analyzed following either anodal or cathodal stimulation. In both cases there was a group of people who had no overall mean response to TDCS (cluster 1: anodal, $n = 28$; cathodal, $n = 25$) and a second group with a mean facilitatory response (cluster 2: anodal, $n = 25$; cathodal, $n = 28$) (Fig. 2A, B). Figure 2C and D plot the mean (non-normalized) data from these two groups. In the anodal session, a one way ANOVA showed a significant main effect of TIME in cluster 2 ($F = 6.8$; df 7, 192; $P < 0.001$), but not in cluster 1 ($F = 0.3$; df 7, 216; $P = 0.930$) (Fig. 2C). Same was true for the cathodal condition (cluster 1: $F = 1.2$; df 7, 192, $P = 0.321$; cluster 2: $F = 3.0$; df 7, 216; $P < 0.001$) (Fig. 2D).

Finally, we tested whether the TDCS responses correlated with any of the baseline measures we had collected (Fig. 1D). Manhattan plots in which we have set the significance level at $P = 0.00132$ in order to correct for multiple possible comparisons, revealed there were two significant factors. AP-LM latency difference was correlated with anodal TDCS effects, and baseline MEP sizes were marginally correlated with both TDCS effects. Other factors, such as

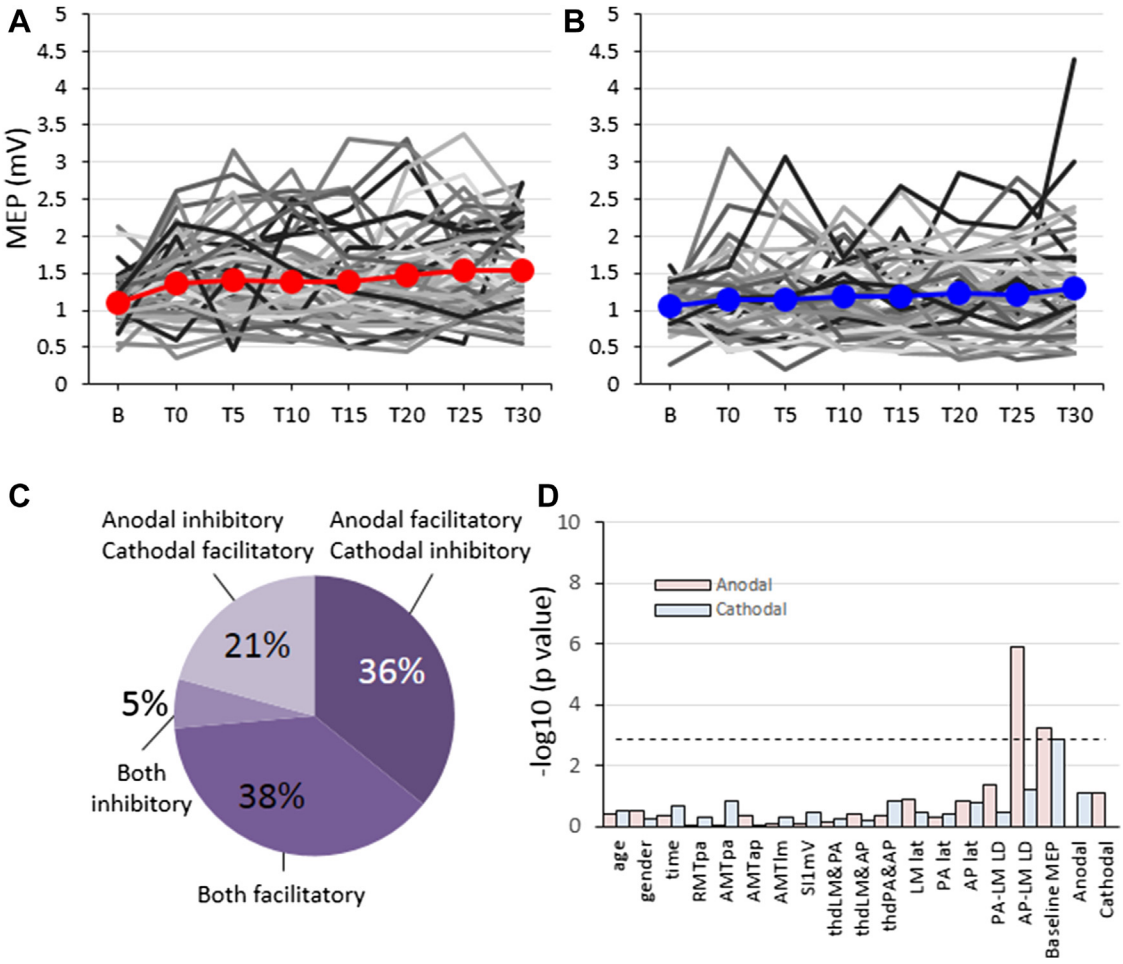

Figure 1. Variability of TDCS. A, B) The time course of after-effects of 2 mA anodal (A) and cathodal (B) TDCS. B, baseline. Dot and thick line indicate the average of each TDCS. Overall, there was only significant increase of MEPs by anodal TDCS. C) Response profile of TDCS. D) Manhattan plot of measured variables. Time, the time of the day; thd, threshold difference; LD, latency difference. Dotted line indicates significant level by Bonferroni's correction.

age (anodal, $P = 0.40$; cathodal, $P = 0.33$), gender (anodal, $P = 0.30$; cathodal, $P = 0.58$), time of day (anodal, $P = 0.45$; cathodal, $P = 0.22$) did not reach significance. Figure 3 plots the relationship between responses to TDCS and the AP-LM latency difference or the baseline MEP size. As described previously by Hamada et al. [10], MEP onset latencies to LM TMS pulses had a shorter latency than those to AP stimulation (Table 1). The difference between the two ranged from 0.2 to 5.9 ms and was highly variable between individuals consistent with the previous study [10]. The mean response to anodal TDCS could be predicted by the AP-LM latency difference ($r^2 = 0.37$; $P < 10^{-6}$) (Fig. 3A), but this was not the case for the response to cathodal TDCS ($r^2 = 0.07$; NS) (Fig. 3B). Anodal effects also correlated with baseline MEP sizes (anodal, $r^2 = 0.21$; $P = 0.00059$) (Fig. 3C), while there was borderline significance for a correlation with baseline MEP sizes in the cathodal condition ($r^2 = 0.18$; $P = 0.00141$) (Fig. 3D). A similar small effect was also noted in the cluster analysis: there were significant differences between clusters in the size of baseline MEPs (anodal, unpaired *t*-test (two-tailed), $P = 0.01$: cathodal, $P = 0.02$) (Fig. 2C, D).

Discussion

As far as we know this is the first large scale prospective study of the variation in after-effects of a TDCS protocol in healthy young volunteers. It was an exploratory study and for pragmatic reasons we chose to examine only one particular variety of TDCS with fairly typical choices of intensity (2 mA), duration (10 min), electrode montage (large bipolar cephalic) and target site (primary motor cortex). We used an intensity of 2 mA, which is higher than that used in most early TDCS studies [1–3,7,8,26], because it seems to be becoming a "standard" intensity in the growing literature of TDCS effects on behavioral and cognitive function and even in clinical settings [1,18,20,27,28]. The results were surprisingly variable: after anodal TDCS, about three-quarters of individuals showed facilitation, and one quarter inhibition, whereas after cathodal TDCS the proportions were approximately 60:40 (facilitation: inhibition). Grouping individuals by whether the mean post-TDCS MEP is larger or smaller than baseline is somewhat arbitrary since in many cases the degree of change is very small and probably of questionable functional relevance. Because of this we also applied a two-step cluster analysis to test for possible groups of individuals with a similar post-TDCS time course. This revealed two main groups after either anodal or cathodal TDCS: there was no mean overall effect in the half of individuals, whilst the other half of people showed facilitation/inhibition. The main conclusion is that the after-effect of this type of TDCS on corticospinal excitability is highly variable. From a practical viewpoint, the data can also be used to estimate sample sizes for subsequent tests using the protocol. For example, if we had two groups of individuals (e.g. patients, controls) and expected that the response in the patient group to anodal TDCS was

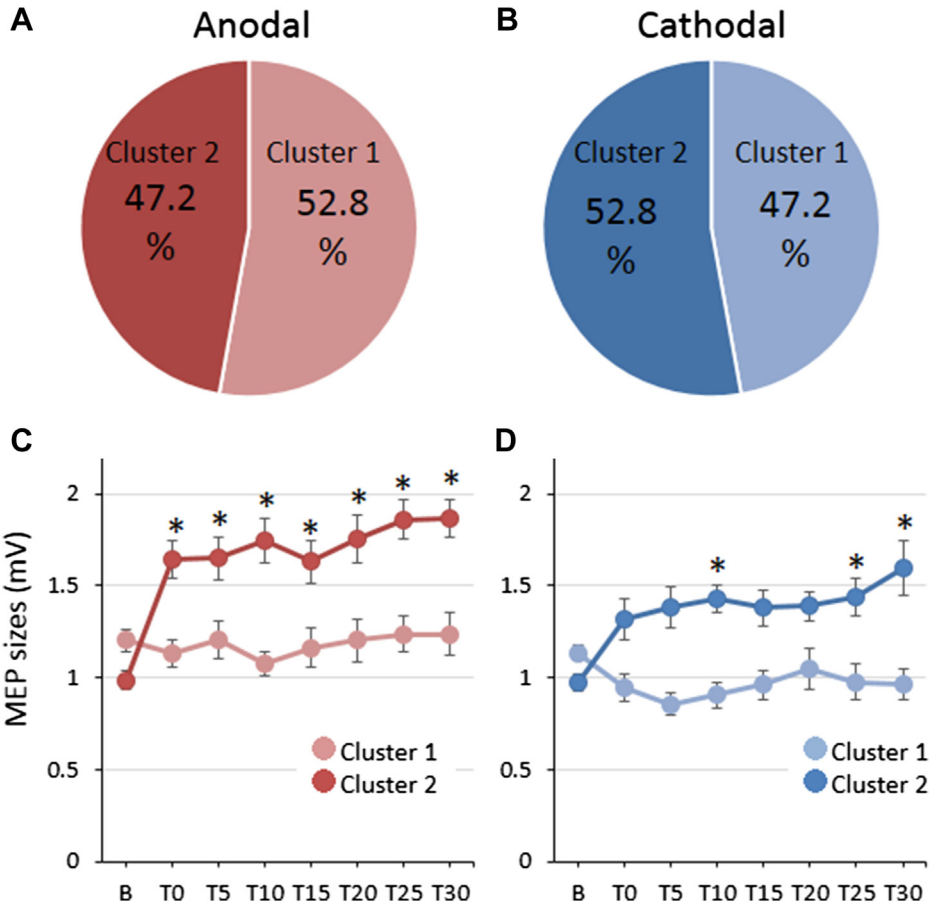

Figure 2. The results of a two-step cluster analysis. A, B) The frequency distribution by cluster analysis in anodal (A) and cathodal (B) sessions. C, D) Time courses of anodal (C) and cathodal (D) TDCS after-effects in each cluster. Error bars indicate standard error. In both sessions, there was significant increase of MEP sizes in cluster 2. Asterisks indicate significant differences of MEP sizes from baseline MEP (after Bonferroni's correction).

going to be approximately half of that of controls (i.e. controls, fractional increase over baseline MEP = 1.4; patients, 1.2), then we would need 87 people in each group to have sufficient power to detect the difference with 95% confidence and 80% power. Note that this calculation is not applicable to studies of repeated measures on the same group of individuals (e.g. ± a drug treatment). We only studied the response to each type of TDCS in one session. We did not repeat the tests in the same individuals on several occasions. Thus it is not clear whether the variability we observed was mainly due to variation between individuals or session-to-session variation within each person. As far as we know there are no studies of this using TDCS protocols.

It is important to note that there is an infinite way in which the TDCS parameters can be combined, so that the results of this study may not apply equally well to all paradigms. In fact, there are quite a few studies in which 1 mA TDCS produces bidirectional changes of cortical excitability in a polarity dependent manner [1–3,7,8,26]. Nevertheless, it is interesting to note that similar assessments of the variability of the excitatory PAS25 protocol [9,11,29–32], 1 Hz rTMS [33], and theta-burst TMS [10,12–15,34] all give similarly variable results in which one third to one half of participants fail to respond in the "canonical" manner. In the absence of other evidence we suggest that it may be worthwhile obtaining similar data for other forms of TDCS.

There is one previous study of responses to TDCS in a large group of young healthy volunteers [8]. However this was a retrospective study from one laboratory that combined baseline data from several different experimental designs (e.g. effects of drug treatments or behavioral learning). The authors reported effects of bipolar TDCS on cortical excitability using 1 mA with a duration of either 13 min (anodal: 73 individuals) or 9 min (cathodal: 74 individuals) [8]. It is difficult to compare the data with the present results since few numerical data are given. However, in our data, the average SD (across all participants) of the normalized post-TDCS time points was 0.55 for anodal and 0.65 for cathodal TDCS. In the data from Kuo et al. [8], we estimate that the mean SE of the graphical data is about 0.07. With 70 + individuals this corresponds to an SD of 0.58, which is very similar to the results reported here.

Subdividing individuals according to their grand average (GA) response removes information about the time course of any TDCS effect. It could be for example that there are groups of individuals who have an early positive response that is balanced by a later negative response. We therefore examined the temporal pattern of all participants in some detail (see Supplementary Material 1). Although some individuals with a GA of around zero had large (or small) responses at individual time points, there was no tendency for individuals to cluster into groups of early/late, or late/early responders. Indeed, the time courses appeared to be essentially random. Effectively, this is in agreement with the cluster analysis since this method should identify individuals who share similar time courses. Nevertheless, to answer such questions definitively would require a larger number of participants, and at the present time we cannot draw any firm conclusion regarding time course from our dataset.

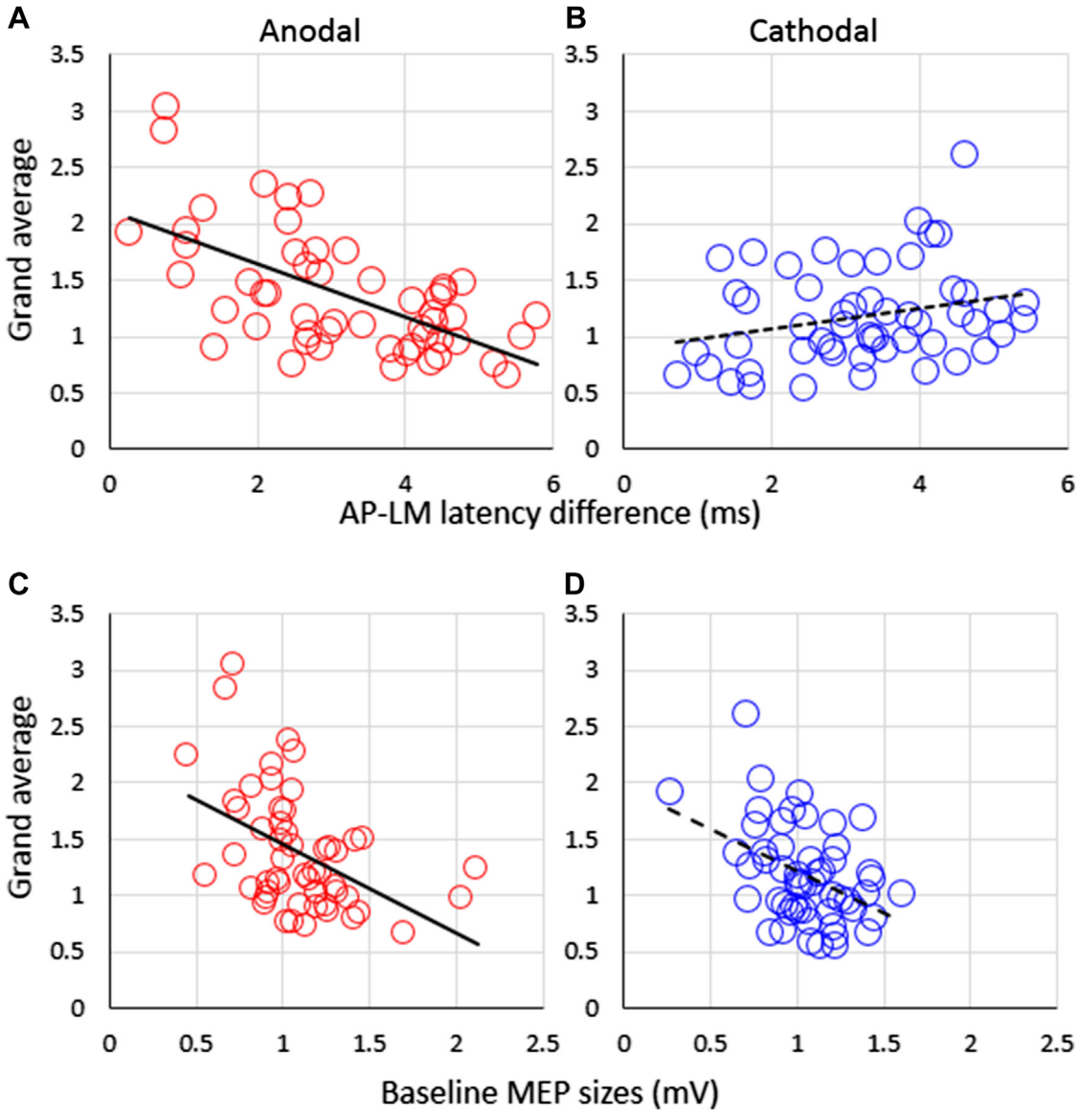

Figure 3. Correlation between TDCS after-effects and AP-LM latency difference (A, B) and baseline MEP sizes (C, D). A) and C), anodal; B) and D), cathodal session.

Hamada and colleagues had previously reported similar variability in the after-effects of two TBS protocols and found that it was related to the latency of MEPs evoked in actively contracting muscles by monophasic anterior–posterior (AP) induced currents in the brain [10]. When they expressed the AP latency relative to the minimal direct wave (D-wave) latency, estimated by direct stimulation of corticospinal axons with high intensity latero-medial (LM) currents, they found that individuals in whom AP stimulation produced MEPs with the longest onset latency were more likely to respond in the "canonical" way to TBS [10]. They argued that the long latency was due to activation of late indirect wave (I-wave) inputs to corticospinal neurons [21] and that these inputs were critical for producing the after-effects of TBS [10]. Recent work has emphasized that late I-inputs might also play an important role in producing the after-effects of PAS protocols [35,36].

The present data showed that there was a moderate correlation between AP latencies and the response to anodal TDCS, such that people with early AP responses were more likely to have an excitatory response to anodal stimulation. Given that AP-LM latency is a surrogate measure of I-wave recruitment [10,21], this means that people in whom early I-waves or D-waves are likely to be recruited by TMS show the "expected" response to anodal TDCS. This is in line with the previous observation that anodal TDCS likely enhances all I-waves including the early ones [22] or even the D-wave [23]. We can only speculate on the possible mechanism linking I-wave recruitment to the anodal effect. Anodal TDCS depolarizes the cell bodies of pyramidal neurons and it may be that this favors LTP-like effects on synapses located on the cell body or on proximal dendrites [37–42]. It has been suggested that early I-inputs target these regions of the pyramidal neuron, so that people in whom early I-inputs are recruited by TMS may be those most likely to show facilitatory after-effects.

It is less clear why there was no correlation of the AP-LM latency difference with the response to cathodal TDCS. However, the situation is complicated by the fact that 1 mA cathodal TDCS has been reported to suppress corticospinal excitability whereas 2 mA, as used here, may either increase excitability [18] or have no effect (present data). The reasons for this difference are unknown, and could involve explanations as diverse as the rates of calcium influx into pyramidal neurons or spread of effective current to connected

brain regions [18]. Nevertheless if multiple mechanisms are involved in the response to cathodal TDCS, then the less likely it is that any single mechanism will correlate with the overall after-effects.

One puzzling result was the borderline correlation between the effect of TDCS and baseline MEP size: participants who had a small baseline MEP were more likely to have a facilitatory response to either anodal or cathodal TDCS. One possibility is that it may be easier to make a smaller baseline MEP larger and vice versa. However, the size range of the baseline MEPs was limited (mostly 0.5–1.5 mV) so that it is unclear why this occurs. If confirmed in subsequent studies, it may be important practical information that the baseline MEP sizes need to be carefully controlled whenever we assess motor cortical excitability. Nevertheless, it seems likely that the source of variability in response to TDCS is multifactorial [17]. It may be possible to simplify these into two groups: intrinsic and extrinsic. Intrinsic variability may relate to factors that are impossible to modify, such as age, gender, and genetics. Extrinsic variability is potentially controllable and includes factors such as detection of the motor hotspot, stability of holding coil, the attention level of subjects in a long experiment, etc.

Although we did not include a sham condition, we can estimate the variability expected in post-TDCS time points if no intervention had occurred (see Supplementary Material 2). Extrapolating from the baseline (pre-TDCS) data, we would expect that more than 95% of all normalized time points should have values lying between 0.7 and 1.3 (i.e. a mean value of 1.0 with 2 SD = 0.3). In fact, 66% of the data in the non-responder group identified by cluster analysis lay within this range, suggesting that TDCS may have increased variability in the amplitude of MEPs. However, it should be noted that this simple calculation assumes that there are no time dependent changes in baseline MEP variability, and therefore the question should be addressed more fully in further experiments. Furthermore, several other potential factors which might play a major role in terms of variability, such as ethnicity, current density, direction of current flow, thickness of bone could also be addressed in future studies.

Conclusion

The effects of TDCS are highly variable, as in other plasticity-inducing protocols, with around 50% of individuals having poor or absent responses. We do not know if these results can be extrapolated to measures other than corticospinal excitability, such as the effects of TDCS on motor learning. However, it would be important to test this in future studies, particularly those in which TDCS is being used to treat neurological conditions. If half of the recruited participants are unlikely to respond to TDCS, it will severely hamper attempts to assess treatment effectiveness.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2014.02.003.

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