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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].