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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.