# A Pilot Study on Effects of 4x1 High-Definition tDCS on Motor Cortex Excitability

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*Abstract*— **High-Definition transcranial Direct Current Stimulation (HD-tDCS) using specialized small electrodes has been proposed as a focal, non-invasive neuromodulatory technique. Here we provide the first evidence of a change in cortical excitability after HD-tDCS of the motor cortex, using TMS motor evoked potential (MEP) as the measure of excitability. Stimulation for 20 minutes at 1 mA with an anode centered over the hand area of the motor cortex and four surrounding return electrodes (anodal 4x1 montage) produced a significant increase in MEP amplitude and variability after stimulation, compared to sham stimulation. Stimulation was well tolerated by all subjects with adverse effects limited to transient sensation under the electrodes. A high-resolution computational model confirmed predictions of increased focality using the 4x1 HD tDCS montage compared to conventional tDCS. Simulations also indicated that variability in placement of the center electrode relative to the location of the target (central sulcus) could account for increasing variability. These results provide support for the careful use of this technique where focal tDCS is desired.**

## I. Introduction

Transcranial Direct Current Stimulation (tDCS) is emerging as a promising tool for the treatment of neuropsychiatric disorders [1] and to facilitate recovery after brain injury and stroke [2]. tDCS is conventionally directed to the cortical target by placing a large active electrode (typically 35 $cm^2$) over the targeted cortical region and another return electrode over an uninvolved head region or extracephalic location [3] [4] [5]. While clinical and scientific studies using this technique have often produced the desired outcomes [6], imaging [7][8] and finite element modeling studies [9][10] show that conventional tDCS montages produce current flow through diffuse pathways, concentrating current in areas distant from the nominal target. Modeling predicts that replacing the two large electrodes with an array of smaller electrodes can improve targeting [11]. Specifically, a 4x1-ring configuration has been proposed to restrict physiologically effective current to an area within the ring perimeter [9][12]. Advances in electrode design and gel composition allow safe and painless stimulation with reduced electrode contact area and higher current density than that used with conventional electrodes [13][14]. Though a method for focal DC neuromodulation is of significant clinical interest, a first step toward validating this technique is testing if this form of targeted stimulation can achieve neuronal excitability changes comparable to what has been demonstrated with conventional montages. Modulation of TMS-induced MEPs represents a standard tool to assess the cortical effect of tDCS

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## II. Methods

*Subjects:*

Ten right-handed, healthy volunteers (seven males) aged 22-37 years (mean age 28.4 $\pm$ 6.3 years) participated in the experiment. All subjects gave written informed consent for the study, which was approved by the CNS Institutional Review Board of the National Institutes of Health. Subjects were interviewed and examined by a neurologist and found to be free of psychiatric or neurological disorders or potentially confounding medications.

*Transcranial Magnetic Stimulation of motor cortex to elicit motor evoked potentials (TMS-MEP):*

Participants were seated comfortably in a chair with the right arm resting on a cushion throughout the experiment. The left motor cortical representational field (hotspot) was identified by single pulse TMS positioned to elicit the largest motor evoked potential (MEP) amplitude from the right Abductor Pollicis Brevis (APB). The TMS stimulus intensity for pre-tDCS MEP measurements was adjusted to produce MEPs of approximately 1 mV peak-to-peak amplitude. Ninety pre-tDCS MEPs were recorded at 0.25 Hz (6 minutes) and 180 post-tDCS MEPs (or post-sham tDCS see below) were recorded at 0.25 Hz (12 minutes) with the same intensity and location. TMS was delivered through a figure-eight coil (70 mm) connected to a Magstim 200 stimulator (The Magstim Company Ltd, Whitland, Wales, UK). The electromyogram was recorded using surface electrodes in a belly-tendon montage. The analog signal was amplified (1 K) and filtered (band-pass 90 Hz to 1 KHz; Coulbourn Instruments, Whitehall, PA), digitized at 2 KHz (Micro 1401, Cambridge Electronics Design, Cambridge, UK) and analyzed offline using Signal software.

*High-definition transcranial DC stimulation (HD-tDCS):*

After baseline TMS recording, tDCS was delivered through a battery-driven constant current stimulator (Schneider Electronic, Gleichen, Germany) connected to a HD-tDCS adaptor device (Soterix Medical Inc. SMI , New

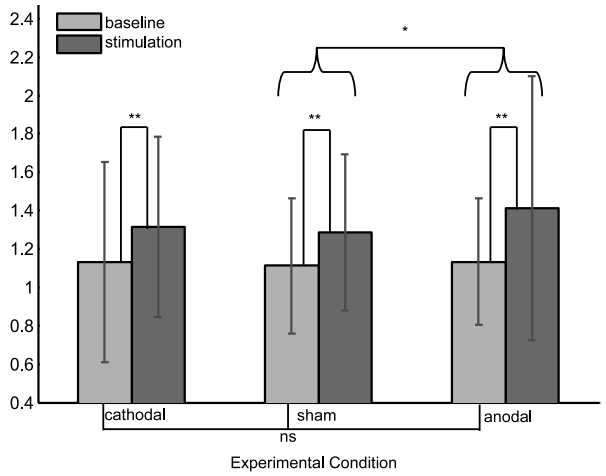


Fig. 1. Modulation of TMS evoked MEP amplitude by 4x1 HD-tDCS. TMS was used to activate the right Abductor Pollicis Brevis (APB) before (baseline) and after each experimental condition (cathodal, sham, anodal). There was no difference across experimental conditions in average MEP amplitude at baseline. All conditions resulted in an increase in MEP amplitude during the time-course of the experiment. Anodal stimulation produced a significant increase in MEP amplitude compared to sham stimulation, with a notable increase in variability ($*P < .05$, $**P < .001$). Whiskers represent standard deviations.

York, NY). Sintered Ag-AgCl electrodes were attached to High-Definition plastic holders (SMI) filled with conductive gel, embedded in an electroencephalogram (EEG) cap and attached to the adaptor device. High-Definition electrodes [13] were arranged on the skull according to a 4x1-ring configuration suggested by modeling [9] with the central electrode placed over the APB hotspot. The return electrodes were spaced 5 cm radially around the active electrode at the corners of a square. The polarity was defined by the active electrode. The current was delivered with a ramp-up time of 10 s, held at 1 mA for 20 min, and then ramped down over 10 s. In the sham condition, current was ramped up and down at the beginning and end of the 20 min period. After tDCS, the cap and stimulating electrodes were removed and 180 MEPs (12 minutes) were recorded using the same settings as for the baseline measurement. All subjects participated in at least one session each of anodal, cathodal, and sham tDCS in different sessions, separated by at least 24 h. A total of 21 anodal, 10 cathodal, and 10 sham sessions were performed. Some subjects reported a sensation under the electrodes, which usually faded a few minutes after current was turned on. This was typically described as itching or tingling. No subject requested that stimulation be aborted and there were no apparent or reported adverse effects.

*Data analysis of TMS-MEPs:*

For each session, the effect of treatment on MEP amplitude was measured by averaging the post-stimulus MEPs and normalizing the result to that of the pre-stimulus baseline for that session. The mean and standard deviations of the effect size were then calculated, and Welschs t-tests (unpaired, two-tailed) were used to analyze the significance of the effects (after being log transformed to pass Lilliefors normality test).

*Computational model of current-flows in the brain:*

Induced electric fields were modeled via a high-resolution MRI derived head model developed previously by our group [15] to assess the focality, generated brain current flow intensity, as well as polarity of stimulation on the hand motor area as a function of electrode position. In addition to the experimentally used HD montage we modeled the conventional C3-SO montage (4x4 $cm^2$ electrode pads). Current densities corresponding to 1 mA total current were applied for each of the aforementioned montages. The Laplace equation was solved (as in [9]) and cortical surface electric-field magnitude and directional maps were plotted (see Figure 2). Magnitude maps represent the total field magnitude regardless of orientation on the cortical surface. Orientation maps represent the cosine of the angle between the field and the normal to the cortical surface [16].

## III. Results

Anodal HD-tDCS at 1 mA increased MEP amplitude after 20 minutes of motor cortex stimulation, compared to sham. Cathodal HD-tDCS at 1 mA for 20 minutes had no significant effect compared to sham. Specifically, there were significant differences between baseline and each post-stimulation/post-sham magnitude (see Figure 1). Average effect sizes relative to trial-paired-baseline values were 45.3% for anodal, and 26.7% for cathodal stimulation, but there was also a considerable effect for the sham condition with 18.2% (c.f. [17]). However, the 58.8% increase in effect size from sham to anodal (t=2.0871, df=41, p=0.0435) supports our hypothesis for anodal HD-tDCS modulation (see Figure 1). Interestingly, the standard deviation (variability in effect size) for the anodal condition (140.5%) was larger than for the cathodal (39.9%) or sham (26.5%) conditions. In fact, only the variance of the anodal magnitudes was significantly different from baseline (p=0.0018, df=42, using a $\chi^2$ variance test post-hoc). A high-resolution computational model confirmed previous results [9] that HD-tDCS using the 4x1 montage results in inward current flow on gyri underneath the center anode, with significant magnitudes restricted to the cortical surface circumscribed by the surrounding return electrodes (see Figure 2, HD-tDCS). A conventional tDCS montage, with two 4x4 $cm^2$ electrode pads, produces diffuse bi-directional current flow across the cortex including significant current flow through brain regions between electrodes (see Figure 2, Conventional tDCS). With the spacing of return electrodes used in this study, peak magnitudes are about half of that achieved with conventional montages for the same total applied current. For both conventional and 4x1 HD-tDCS montages the direction of current flow into the brain is complex, with significant changes in magnitude and direction across opposite walls of sulci. Specifically, placing the center electrode anteriorly versus posteriorly over the central sulcus can lead to a change in polarity at the anterior wall of the central sulcus, which corresponds to the hand motor area ([18], see region outlined with dotted line on the right column of Figure 2).

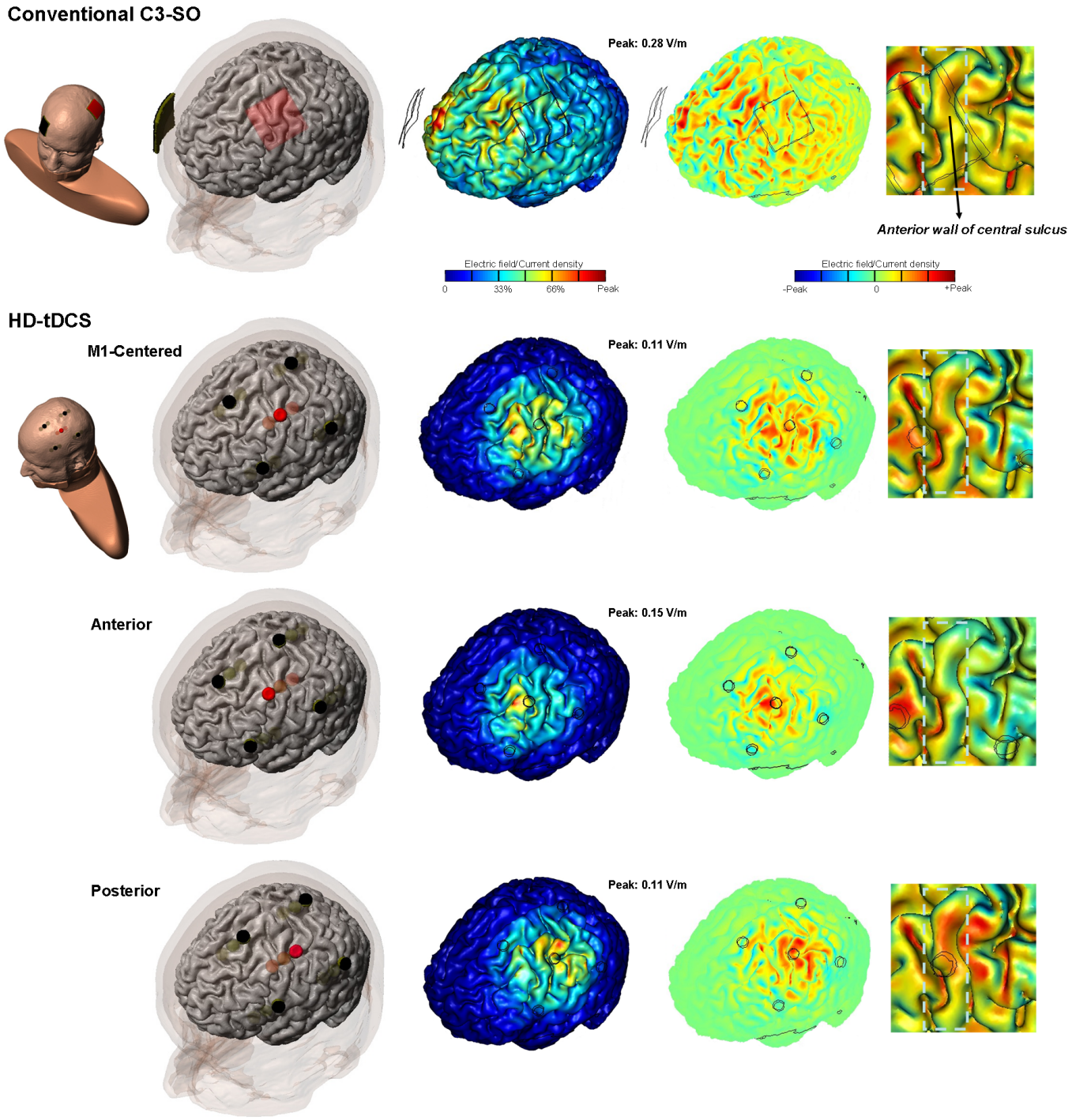


Fig. 2. Predicted magnitude and polarity for conventional and HD-tDCS montages. Computational models predict targeted brain current flow with High-Definition-tDCS in comparision to conventional tDCS. The HD 4x1 montage consisted of one anode surrounded by four cathodes at 5 cm distance from the center electrode. The conventional sponge montage used one anode centered over C3 and one cathode over the contralateral supra-orbital region (top row) both electrodes were 4 cm x 4 cm in size. In the HD 4x1 configuration the center electrode was either placed directly over the left central sulcus (second row), anteriorly to the central sulcus (third row), or posteriorly (fourth row). Electric field magnitude (left) and electric field normal to the cortical surface (right and inset) were considered. HD- tDCS resulted in brain current flow that is restricted to within the ring perimeter with dominant inward current on gyri. Polarity of current on the wall of the central sulcus depended on location of the anodal center electrode, with inward (anodal) stimulation for posterior placement and outward (cathodal) current for anterior placement. Conventional tDCS resulted in comparatively diffuse current flow with clusters of peaks and bidirectional stimulation on opposing walls between the electrodes (not under the electrodes). The anterior wall of the central sulcus underneath the anodal sponge receives predominantly inward (anodal) stimulation.

## IV. Discussion and Conclusions

Our data confirmed that 20 minutes of 1 mA anodal HD-tDCS using the 4x1 configuration is sufficient to elicit a significant increase of MEP amplitudes compared to sham. The direction of change was consistent with conventional tDCS, while the weak magnitude of modulation is consistent with 1 mA 4x1 HD-tDCS (at 5 cm radius) producing peak brain currents comparable with only 0.5 mA conventional tDCS [9]. This study confirms the safety and tolerability of HD-tDCS [13][19], and provides the first direct evidence for cortical neuroplasticity using this novel non-invasive neuromodulatory technology; however, fundamental questions remain to be addressed concerning the optimization of HD-tDCS dose. Conventionally, anodal and cathodal tDCS are expected to increase and decrease MEP amplitude, respectively [20][21]; however, both the direction and magnitude of modulation are complex functions of stimulation intensity[21][20], duration [20][22][21], the activation state of the underlying cortex, and cortical anatomy. We show that both conventional and HD-tDCS produce complex brain current flow with local clusters of peak intensity [9] and interspersed bi-directional current flow (see Figure 2). This provides a possible explanation to some of the mixed results previously reported with the conventional montages [20][21][22]. In this study using 4x1 HD-tDCS, the variability following anodal stimulation was greater than sham by more than a factor of 5. Modeling confirmed that overall current-flow on gyri underneath the center electrode is unidirectional; however, displacement of this electrode relative to the location of a sulcus can lead to a reversal in polarity on the wall of the sulcus. Since the hand motor area lies on the anterior wall of the central sulcus, this may explain some of the large increase in variability observed here for anodal stimulation. Future studies using the 4x1 configuration should use care in placing the center electrode when the cortical target is expected to lie within a cortical fold. Note that the TMS current flow which elicits MEPs is exclusively tangential to the surface of the head. Indeed, optimal tangential stimulation may be achieved with a bipolar electrode configuration across the targeted sulcus [11]. HD-tDCS can be employed in a wide range of configurations (e.g. 4x2, 2x2.; see [11] for description of subject-specific optimization of radial fields); and even within the 4x1 montage, varying electrode center position, ring diameter, stimulation polarity, duration and amplitude represents a large parameter space. As a proof of concept, the present study only evaluated one configuration at a given current intensity. Though the small effect size with 1 mA HD-tDCS was expected, this first demonstration of a significant lasting change in neuronal excitability provides motivation for further studies. The safety and tolerability of 4x1 HD-tDCS with up to 2 mA of current are supported by recent clinical studies [13][19] and our in-house experience.

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