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Effects of electrode angle-orientation on the impact of transcranial direct current stimulation on motor cortex excitability

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ABSTRACT

Background: For effects of transcranial direct current stimulation (tDCS), electrical field distribution and coverage of the target areas play a decisive role.
Methods: We explored the effect of different angle-orientations of tDCS electrodes applied over the upper limb motor cortex (M1) on motor cortex excitability in healthy volunteers. Sixteen individuals received 1 mA anodal or cathodal tDCS through 35 cm^2 electrodes over M1 for 15 min. Transcranial magnetic stimulation was used to examine tDCS-generated cortical excitability effects. The M1 electrode-orientation was following the right-left longitudinal plane, or positioned with 45° deviation from the midsagittal plane. Coverage of underlying brain and electrical field orientation were also investigated.
Results: Cortical excitability modulation was observed only when the electrode was aligned with 45° angle, which covered a larger area of the motor cortex.
Conclusion: an electrode angle-orientation of 45° induces superior neuroplastic effects of M1 due to a better alignment with the motor cortex.

Introduction

Transcranial direct current stimulation (tDCS) induces changes of cortical excitability and modulates cognition and motor processes [1–3]. tDCS alters excitability [4,5] via changes in neuronal firing by hyperpolarizing or depolarizing brain tissue, and glutamatergic plasticity [6,7]. The efficacy of tDCS hereby depends on different stimulation aspects, such as current density/flow direction, electrode size/placement/configuration, stimulation duration, and combination with task performance or rehabilitation therapy [8].

For alteration of neuronal membrane excitability, alignment of electrical field orientation with the long axis of a given neuron is mandatory [8,9]. Compared to rodent and slice studies [10–12], due to its gyrated cortex, and heterogeneous orientation of neurons, stimulation effects are assumed to be more heterogeneous in humans [10,11]. However, at the population level, similar effects as in animal experiments have been obtained [12–14]. The position of the electrode over the targeted region, but also the return electrode position, which together determine electrical field orientation, are critical for the efficacy of tDCS [13,14].

Furthermore, electrode size and geometry are relevant for the formation of the electrical field. Smaller electrodes deliver more specific effects [15,16]. Since tDCS modulates also functional connectivity at the cortical network level [17], covering a larger area of connected regions could enhance efficacy of tDCS. This was recently shown for the motor cortex model [18].

We explored the impact of different angles of a conventional electrode positioned over the primary motor cortex on tDCS-induced cortical excitability alterations. We hypothesized that alignment of the long axis of the electrode with the central sulcus (which is the electrode orientation used in our laboratory) results in better effects than an electrode orientation with the long axis along the medio-lateral axis. The former electrode orientation should cover the primary motor cortex, and also connected areas, to a larger degree than the latter. We investigated the

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neurophysiological effects of these electrode orientations on upper-limb motor cortex excitability of healthy individuals.

Methods

Subjects

Sixteen (10 women, 25.32 ± 4.3 years old) healthy right-handed individuals participated in this study, which was performed in accordance with the Declaration of Helsinki and approved by the local ethics commission of the Leibniz Research Center. Participants were financially compensated. Exclusion criteria comprised CNS-active medication, history of brain disorders, contraindications for tDCS/TMS, and tobacco smoking. The volunteers were instructed not to practice sport activities, and not to consume alcohol during 24 h, or caffeine during 2 h before the start of the experiment.

Experimental procedures

Experimental design

The study was randomized, cross-over, and single-blind. Anodal and cathodal tDCS were applied in different sessions with different electrode angle-orientations over the upper-limb motor cortex (M1). The effects of tDCS were monitored by TMS-evoked MEP at baseline and up to 120 min after tDCS (Fig. 1A).

MEP recording

TMS was applied to the left upper-limb primary motor cortex with a figure-of-eight coil connected to a PowerMag 100 ppTMS stimulator (Mag&More, Germany). The coil was placed in a posterior-anterior direction, and the handle of the coil pointed backwards at an angle of 45° from the midsagittal plane. The motor hotspot was defined as the coil position resulting in the largest MEP amplitude of the right abductor digiti minimi muscle (ADM), and was marked with a pen to allow constant coil position. TMS intensity (percentage of maximum stimulator output, %MSO) was determined to achieve a baseline MEP amplitude of 1 mV and kept constant throughout the experimental session. Twenty-five MEP were recorded in each time bin.

tDCS

tDCS was applied through a pair of 7 × 5 cm electrodes via a StarStim stimulator (NeuroElectrics, Spain) with 1 mA current strength for 15 min, with 10 s ramping-up and -down. The following tDCS protocols were applied: (i) anodal – longitudinal; (ii) cathodal – longitudinal; (iii) anodal – 45°; and (iv) cathodal – 45°. Longitudinal and 45° refer to the angle-orientation of the M1 electrode. The longitudinal electrode was positioned along the coronal anatomical plane (long axis medio-lateral), and the other with a 45° rotation angle in relation to the midsagittal plane (Fig. 1B). The return electrode was placed above the contralateral supraorbital region. Saline-soaked surface sponge electrodes attached by elastic bands were used, and the connector cable left the electrodes on the side pointing backwards (Fig. 1B).

Finite element modeling

SimNIBS, which uses FreeSurfer and FSL BET to segment the head, was employed for modeling electrical current distribution [19,20]. We determined coverage of the motor and premotor regions (Fig. 2A), defined current flow direction, and calculated the

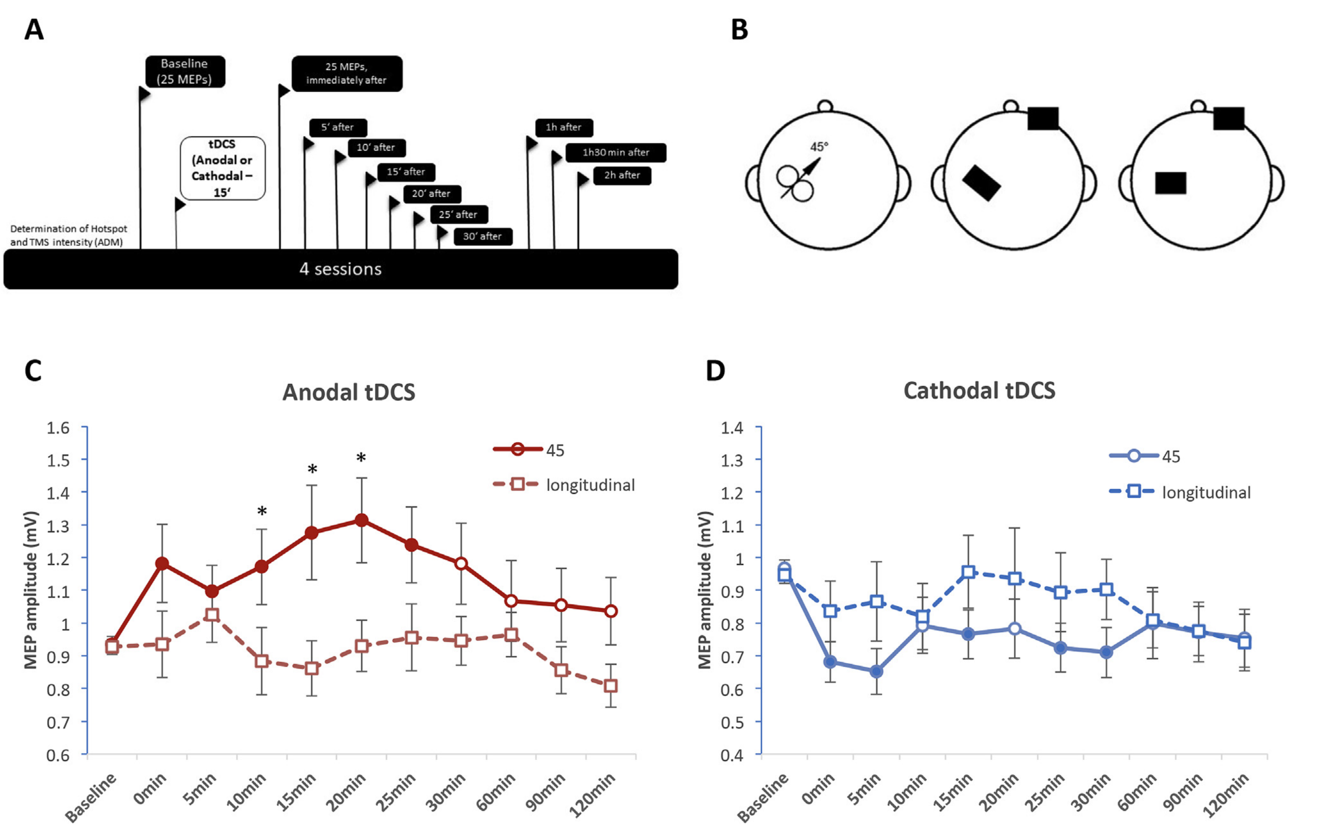


Fig. 1. Experimental design and results of cortical excitability alteration following tDCS. MEP amplitudes deviating more than ±2 standard deviations from the individual mean and with pre-TMS muscle artefacts were excluded. **(A)** Experimental design **(B)** Electrode angle-orientation. **(C)** Anodal tDCS effects on MEP amplitudes, absolute values. **(D)** Cathodal tDCS effects on MEP amplitudes, absolute values. Filled symbols indicate significant difference to baseline. Asterisks represent significant difference between two angle orientations for each polarity. ($p < 0.05$). The error bars denote standard errors of the mean.

difference between the norm values of the electric fields (normEF) (for details, see Fig. 2).

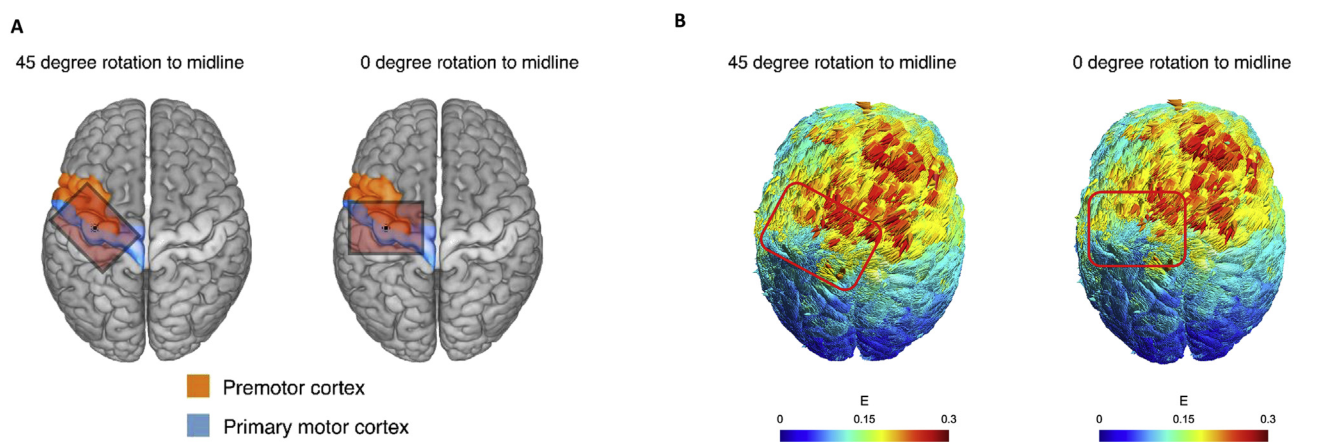
Statistical analysis

Individual means of 25 MEP amplitudes were calculated for all subjects and time bins. MEP amplitudes deviating more than ±2 standard deviations from the individual mean and with pre-TMS muscle artefacts were excluded. A two-tailed paired-sample Student's *t*-test was conducted to evaluate if baseline MEP measures and %MSO of TMS differed between experimental sessions.

A repeated-measures ANOVA was performed with absolute MEP amplitudes as the dependent variable, and electrode angle-orientation (longitudinal, 45°), stimulation polarity (anodal, cathodal) and time bins (baseline, post0-120) as within-subjects factors. For each tDCS protocol, furthermore a one-factorial repeated measures ANOVA was performed with absolute MEP amplitudes as the dependent variable and ‘time’ as within-subject factor. *Exploratory post hoc* comparisons were performed using *Student's t*-test. One volunteer, due to schedule issues, dropped out, thus the statistical analysis was performed for 15 volunteers. Data were analyzed with SPSS (Statistical Package for Social Sciences) version 25.0 for Windows (SPSS Inc., Chicago IL). A P value < 0.05 was considered significant for all statistical analyses.

Results

Baseline MEP and %MSO show no significant difference between sessions. The 3-factorial repeated-measure ANOVA reveals significant ‘orientation x polarity x time’ ($F(10, 140) = 1.981$, $p = 0.040$), ‘orientation x polarity’ ($F(1, 14) = 8.359$, $p = 0.012$), and ‘polarity x time’ ($F(1, 14) = 1.985$, $p = 0.039$) interactions, and a significant effect of ‘polarity’ ($F(1, 14) = 7.497$, $p = 0.016$). The one-factorial ANOVAs conducted for all tDCS protocols separately show significant effects of ‘time’ for the 45°-orientation protocols (anodal: $F(10, 140) = 2.028$, $p = 0.035$; cathodal: $F(10, 140) = 2.210$, $p = 0.020$), but not for the longitudinal conditions. Accordingly, *post-hoc* tests conducted to compare baseline with post-tDCS MEP amplitudes show a significant enhancement after anodal tDCS in the 45° electrode orientation only, which lasted for 25 min after intervention, whereas cathodal tDCS with this electrode position resulted in inhibitory effects. *Post-hoc* tests contrasting angle orientations show significant differences at the time-points post10 ($p = 0.012$), post15 ($p = 0.011$), and post20 ($p = 0.01$) (Fig. 1C and D) for anodal tDCS. In further accordance, higher response rates were observed by tDCS with 45°-oriented target electrodes for both anodal and cathodal stimulation, as compared to the respective longitudinal-oriented stimulation protocol (supplementary material).



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Variable \ Angle		45°	0°
EF (V/m)	ML	-0.285	-0.269
	PA	-0.055	-0.0668
	IS	0.316	0.289
normEF (V/m)		0.473	0.447

EF: electric field, **normEF**: norm value of EF, **ML**: medio-lateral, **PA**: posterior-anterior, **IS**: inferior-superior

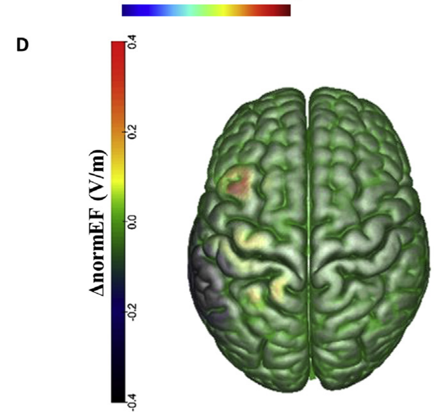

Fig. 2. Results of fine element modeling. Simulation was performed using the standard head model provided by the software (http://simnibs.de/_media/simnibs2.0_example.tar.gz). Size, position, and orientation of the electrodes, and current intensity were adjusted according to the experimental setting. Electric field values were converted to a nifti file using the msh2nii command. **(A)** Test if the motor cortex electrodes differed with regard to coverage of the motor and premotor regions, we created a ROI containing Brodmann areas 4 and 6, the electrode over M1 covers larger parts of M1 and premotor cortex (shown in blue and orange, respectively) if it is rotated by the angle 45°. **(B)** Simulated electrical field vectors for the two different electrode configurations; in both configurations, one electrode (anode, 5 × 7 cm) is placed over the right orbit and the other (cathode, 5 × 7 cm) over the left M1 region, but with the different orientation. Current intensity was set to 1 mA. **(C)** To determine current flow direction, vector components of the average electric field (EF) value for all nodes inside this volume were calculated in three different directions (ML: medio-lateral, PA: posterior-anterior, IS: inferior-superior). The amplitude of electric field and its norm value in the primary motor cortex (M1) and premotor areas (PreM1) for two different angles of the M1 electrode. **(D)** The difference between the values of normEF in the two models shows that preM1 and M1 regions are more strongly affected with the 45° rotated electrode. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

EF values for the two models are shown in Fig. 2B. The amplitudes of EF and normEF values in the M1+PreM1 ROI (Fig. 2C) show stronger EF and normEF induced by the 45° angle electrode. The EF component in the inferior-superior direction is larger with the 45° angle. The difference between the values of normEF in the two models (Fig. 2D) demonstrates that preM1 and M1 regions are affected to a larger degree in the 45°-oriented condition.

Discussion

Several factors contribute to the efficacy of tDCS to induce neuroplasticity of the human brain, including protocol specifics [23]. The relevance of angle-orientation of conventional rectangular stimulation electrodes has been rarely explored so far. The results of the present study show that electrode angle-orientation has a relevant impact. A significant excitability enhancement with anodal, and reduction with cathodal tDCS was observed only when tDCS was applied with an angle-orientation of the M1 electrode of 45° from the midsagittal line.

A presumably important factor for tDCS effects is the dependency of the neuronal excitability change from the axonal orientation relative to the electric field vector, as shown in animal slice models [9,13]. Recent results of human studies imply that the direction of current flow through respective cortical target regions has to be considered for targeting and dose-control of tDCS [24,25]. Directionality of current flow was however not relevantly altered by the different angle of the motor cortex electrodes, and thus cannot account for these results. Since the 45° angle-orientation covers larger parts of the cortical motor network, including the ipsilateral premotor cortex, premotor tDCS affects intracortical excitability of the ipsilateral M1 [21], and stimulation of the cortical motor network alters M1 excitability more efficiently as compared to stimulation over M1 alone [18], this might explain the superior effects of this montage.

Limitations of this study include the small sample size, and a missing sham tDCS condition. The results of this study suggest that the specific placement of the electrodes on the head is crucial for tDCS effects. This stresses the relevance of tDCS protocol specifics for obtained physiological and behavioral effects [22–25].

Conflicts of interest

MAN is member of the advisory board for Neuroelectrics, Spain. None of the remaining authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.10.014.

References

[1] Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 2006;5(8):708–12.

[2] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimulation 2008;1(3):206–23.

[3] Madhavan S, Shah B. Enhancing motor skill learning with transcranial direct current stimulation–a concise review with applications to stroke. Front Psychiatr 2012;3.

[4] Soekadar SR, Witkowski M, Cossio EG, Birbaumer N, Cohen LG. Learned EEG-based brain self-regulation of motor-related oscillations during application of transcranial electric brain stimulation: feasibility and limitations. Front Behav Neurosci 2014;8.

[5] Marquez J, Conley A, Karayanidis F, Lagopoulos J, Parsons M. Anodal direct current stimulation in the healthy aged: effects determined by the hemisphere stimulated. Restor Neurol Neurosci 2015;33(4):509–19.

[6] Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 2002;125(10):2238–47.

[7] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011;17(1):37–53.

[8] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol 2016;127(2):1031–48.

[9] Kabakov AY, Muller PA, Pascual-Leone A, Jensen FE, Rotenberg A. Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. J NeurophysiolJ Neurophysiol 2012;107(7):1881–9.

[10] Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC. Optimized multi-electrode stimulation increases focality and intensity at target. J Neural Eng 2011;8(4):046011.

[11] Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J Physiol 2013;591(10):2563–78.

[12] Antal A, Nitsche MA, Kincses TZ, Kruse W, Hoffmann KP, Paulus W. Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. Eur J Neurosci 2004;19(10):2888–92.

[13] Nitsche M, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(3):633–9.

[14] Parkin BL, Bhandari M, Glen JC, Walsh V. The physiological effects of Transcranial Electrical Stimulation do not apply to parameters commonly used in studies of Cognitive Neuromodulation. Neuropsychologia 2018. https://doi.org/10.1016/j.neuropsychologia.2018.03.030 [Epub ahead of print].

[15] Edwards D, Cortes M, Datta A, Minhas P, Wassermann EM, Bikson M. Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS. Neuroimage 2013;74:266–75.

[16] Nitsche MA, Doemkes S, Karakoese T, Antal A, Liebetanz D, Lang N, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J NeurophysiolJ Neurophysiol 2007;97(4):3109–17.

[17] Polanía R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp 2012;33(10):2499–508.

[18] Fischer D, Fried P, Ruffini G, Ripolles O, Salvador R, Banus J, et al. Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex. Neuroimage 2017;157:34–44.

[19] Windhoff M, Opitz A, Thielscher A. Electric field calculations in brain stimulation based on finite elements: an optimized processing pipeline for the generation and usage of accurate individual head models. Hum Brain Mapp 2013;34(4):923–35.

[20] Thielscher A, Antunes A, Saturnino GB, editors. Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS? Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE. IEEE; 2015.

[21] Boros K, Poreisz C, Münchau A, Paulus W, Nitsche MA. Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans. Eur J Neurosci 2008;27(5):1292–300.

[22] Foerster Á, Rocha S, Wiesiolek C, Chagas AP, Machado G, Silva E, et al. Site-specific effects of mental practice combined with transcranial direct current stimulation on motor learning. Eur J Neurosci 2013;37(5):786–94.

[23] Woods AJ, Bryant V, Sacchetti D, Gervits F, Hamilton R. Effects of electrode drift in transcranial direct current stimulation. Brain stimul 2015;8(3):515–9.

[24] Rawji V, Ciocca M, Zacharia A, Soares D, Truong D, Bikson M, et al. tDCS changes in motor excitability are specific to orientation of current flow. Brain Stimul: Basic Transl Clin Res Neuromodulation 2018;11(2):289–98.

[25] Tremblay S, Hannah R, Rawji V, Rothwell JC. Modulation of iTBS after-effects via concurrent directional TDCS: a proof of principle study. Brain Stimul: Basic Transl Clin Res Neuromodulation 2017;10(4):744–7.