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Effect of transcranial direct current stimulation (tDCS) during complex whole body motor skill learning

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HIGHLIGHTS

- Transcranial direct current stimulation (tDCS) is known to modify motor skill learning.
- Concomitant anodal SMA and cathodal PFC stimulation impairs complex motor skill learning.
- This effect was driven by the cathodal PFC stimulation.
- Location of both tDCS electrodes is important for the outcome of complex motor skill learning.

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ABSTRACT

The aim of the study was to investigate tDCS effects on motor skill learning in a complex whole body dynamic balance task (DBT). We hypothesized that tDCS over the supplementary motor area (SMA), a region that is known to be involved in the control of multi-joint whole body movements, will result in polarity specific changes in DBT learning. In a randomized sham-controlled, double-blinded parallel design, we applied 20 min of tDCS over the supplementary motor area (SMA) and prefrontal cortex (PFC) while subjects performed a DBT. Anodal tDCS over SMA with the cathode placed over contralateral PFC impaired motor skill learning of the DBT compared to sham. This effect was still present on the second day of training. Reversing the polarity (cathode over SMA, anode over PFC) did not affect motor skill learning neither on the first nor on the second day of training. To better disentangle whether the impaired motor skill learning was due to a modulation of SMA or PFC, we performed an additional control experiment. Here, we applied anodal tDCS over SMA together with a larger and presumably more ineffective electrode (cathode) over PFC. Interestingly this alternative tDCS electrode setup did not affect the outcome of DBT learning. Our results provide novel evidence that a modulation of the (right) PFC seems to impair complex multi-joint motor skill learning. Hence, future studies should take the positioning of both tDCS electrodes into account when investigating complex motor skill learning.

1. Introduction

Noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) are capable of inducing bidirectional changes in cortical excitability depending on specific stimulation parameters (for review see [1]), [3]. Furthermore, it has been repeatedly demonstrated that brain stimulation-induced changes in cortical excitability can secondarily influence motor performance and skill learning [2,4–7]. For example, previous studies provided compelling evidence that increasing excitability of the learning primary motor cortex (M1) by means of anodal tDCS (a-tDCS) facilitates motor skill learning [4,8–10] not only during but also after termination of stimulation. On the other hand, cathodal tDCS (c-tDCS) has been shown to impair performance in an explicit sequence learning task [11]. Based on these findings, there is considerable evidence that tDCS over M1 is capable of inducing polarity-specific changes in motor behaviour.

Motor learning has been consistently shown to be associated with a large-scale cortical network that includes areas such as premotor and supplementary motor area, the basal ganglia and the cerebellum [12,13]. While the role of M1 in motor skill acquisition and retention has been extensively studied (for review see [13]), the effects of tDCS outside M1 on motor skill learning still remain

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elusive. Recently, one study provided evidence that the supplementary motor area (SMA) might also play a decisive role in the context of short-term visuomotor sequence learning [6].

With respect to the task characteristics, the majority of studies investigated tDCS-induced changes in motor behaviour using simple models of motor skill learning. However, our daily life requires much more complex motor behaviour including multi-joint arm and/or leg movements as well as the combination of numerous muscular contractions with precise timing. Hence, it is surprising that there are no systematic investigations on the effect of tDCS in daily life situations.

Among other paradigms [14–16] the dynamic balance task (DBT) seems to be a good model for complex motor skill learning as it requires highly coordinated whole-body movements [17]. Previous studies [17] showed that DBT training resulted in dynamic functional and structural brain changes in motor-related regions such as the supplementary and pre-supplementary motor areas (SMA, pre-SMA). SMA in particular seems to be associated with planning of self-initiated or externally generated movements and the initiation and repetition of movements [18–21].

Here we investigated the effect of tDCS over SMA and prefrontal cortex on the performance of a DBT. Using different tDCS polarities, we aimed to explore the role of SMA on complex motor skill learning. In analogy to previous studies using simple models of sequential motor skill learning, we hypothesized that a-tDCS over SMA (cathode over contralateral prefrontal cortex (PFC)) will improve while c-tDCS over SMA (anode over contralateral PFC) will impair complex motor skill learning relative to sham. To further investigate the role of the tDCS "reference" electrode, we also performed a control experiment using a larger, presumably ineffective tDCS electrode over PFC while the anode was placed over SMA.

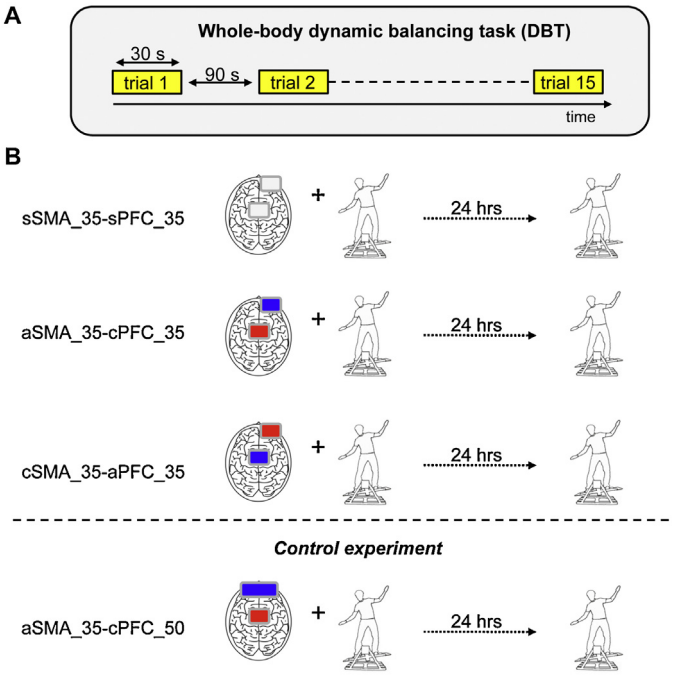

Fig. 1. Experimental setup and design. (A) Subjects performed a complex whole-body dynamic balancing task (DBT) for approx. 20 min. (B) On the first training day (TD 1), subjects received either sham (sSMA_35-sPFC_35), anodal stimulation over SMA and cathodal stimulation over PFC (aSMA_35-cPFC_35) or cathodal stimulation over SMA and anodal stimulation over PFC (cSMA_35-aPFC_35) during DBT performance. On the second day of training (TD 2), subjects performed the DBT without tDCS. As a control experiment, we tested another group of subjects using a 35 cm^2 anodal tDCS electrode for SMA and a larger, presumably more ineffective 50 cm^2 cathodal electrode placed over PFC (aSMA_35-cPFC_50). Red square: anode, blue square: cathode, grey squares: sham tDCS.

2. Methods

2.1. Ethics statement

The study procedures were approved by the local ethics committee of the University of Leipzig. Subjects gave written informed consent to participate in the experiment according to the declaration of Helsinki.

2.2. Design

Here, we used a randomized, double-blinded, sham controlled parallel design, to investigate the effect of tDCS on the performance of a complex whole-body dynamic balancing task (DBT, see also Fig. 1). Subjects were asked to perform the DBT during 20 min of tDCS applied over the supplementary motor area (SMA). On the next day, DBT performance was re-evaluated without tDCS to investigate the reversibility of tDCS-induced effects on the newly acquired motor skill. A total number of 40 right-handed subjects (25.61 ± 3.11 years, 19 females) were included in the study after giving written informed consent. Handedness was assessed by the Edinburgh Handedness Inventory scale [22].

All subjects were free of any medication and were informed about potential risks of brain stimulation prior to the study. Highly skilled subjects such as musicians, typists or sportsmen were not included. Participants were divided into 3 experimental groups ($n = 10$ each, please see also Fig. 1B). In each group, one electrode was placed over the SMA and the other over the contralateral prefrontal cortex (PFC, contralateral orbit). Electrode size was 35 cm^2 each. The only difference between groups was the polarity of DC currents applied: (group A) sham tDCS over SMA and PFC (sSMA_35-sPFC_35, 6 female, 4 male), (group B) anodal stimulation over SMA and cathodal stimulation over PFC (aSMA_35-cPFC_35, 2 female, 8 male) and (group C) cathodal stimulation over SMA and anodal stimulation over PFC (cSMA_35-aPFC_35, 5 female, 5 male).

In 10 additional subjects, a different tDCS montage was used (group D): anodal tDCS over SMA (35 cm^2 electrode) and a larger 50 cm^2 electrode (cathode) over the contralateral orbit (aSMA_35-cPFC_50, 5 female, 5 male, Fig. 1B). With this control experiment we aimed minimize potential influences of the electrode placed over PFC on motor skill learning.

2.3. Whole-body dynamic balancing task (DBT)

The DBT was performed on a movable platform (stability platform, model 16030, LaFayette Instrument, US) with a maximum deviation of 26° to each side. A detailed description of the procedure has been described elsewhere [17]. In brief, subjects were instructed to stand on the platform and to keep it in a horizontal position as long as possible during a trial length of 30 s. On each training day, 15 trials had to be performed with an inter-trial (rest) interval of 90 s to avoid muscle fatigue (please see Fig. 1A). During the time course of DBT learning, subjects had to discover their own strategy to improve task performance.

After each trial, subjects were given verbal feedback about their time in balance (TIB, outcome measure), defined as the individual time of each subject to keep the balance platform in a horizontal position within a range of ±3° to each side during the 30 s trial length. DBT was performed for approximately 28.5 min including rest blocks. tDCS was applied for 20 min. Hence, the experimental task continued after the end of tDCS for another 8.5 min.

2.4. MRI and neuronavigation

All Subjects underwent an anatomical MRI scan acquired on a 3 Tesla scanner (MAGNETOM Trio, Siemens, Erlangen, Germany) before the experiment. The anatomical data were transformed into a 3D-MNI-image by using Brainsight (Brainsight Version 2, Rogue Research Inc., Montreal, Canada). The images were used to identify the respective target area (SMA-proper). SMA-Coordinates were defined as −9, −2, 69 (MNI coordinates *x*, *y* and *z*) according to a previous study from our group [23] and located for each brain individually. After localization of SMA, we marked the point, prepared the skin with alcohol and placed the tDCS electrodes.

2.5. Transcranial direct current stimulation

A weak, direct current of 1 mA generated from a battery driven stimulator (neuroConn GmbH, Ilmenau, Germany) was administered for a total duration of 20 min. For tDCS application, we used highly conductive electrode gel (Ten20 CONDUCTIVE Neurodiagnostic Electrode Paste, Weaver and Company) and the electrodes were fixated by using flexible straps. For aSMA_35-cPFC_35 and cSMA_35-aPFC_35 (group B and C) a current density of 0.028 mA/cm^2 and a total charge of 0.033 C/cm^2 under each electrode (35 cm^2 each) was applied which has been shown to be effective in modulating cortical excitability and motor performance (for review see [1]). It has been a matter of debate, whether the electrode attached over the PFC might also influence task performance. However, at least in simple motor learning paradigms, stimulation of M1 and PFC simultaneously with 35 cm^2 tDCS electrodes usually does not negatively impact motor skill learning (for review see [13]). However, for complex motor skill learning paradigms, brain regions such as the PFC, that are underlying the tDCS electrode, might be affected by tDCS and play a crucial role as well [24,25]. Therefore, we tested another group of subjects (group D) using a 35 cm^2 tDCS electrode over SMA and a larger, presumably ineffective 50 cm^2 electrode placed over contralateral PFC (aSMA_35-cPFC_50,current density for the 50 cm^2 electrode: 0.02 mA/cm^2, total charge of 0.024 C/cm^2).

During tDCS, the current was increased at the beginning and decreased at the end of tDCS for 30 s in a ramp-like fashion as described previously ([4]). During sSMA_35-sPFC_35 current was increased, maintained and decreased for 30 s each. Subjects rated their level of attention (1 = not attentive, 10 = very attentive), perception of fatigue (1 = strong fatigue, 10 = no fatigue) and their level of discomfort (1 = no discomfort, 10 = strong discomfort) before and after tDCS using a visual analogue scale (VAS).

2.6. Data analysis

Data were analyzed using SPSS statistics (version 19). First, in order to investigate complex motor skill learning within each group, repeated measures ANOVAs (ANOVA$_{RM}$) with factor TIME for each group separately were performed to investigate time in balance (TIB) performance over time. Subsequently, ANOVA$_{RM}$ with factor TIME (trial 1-15) and GROUP (sSMA_35-sPFC_35, aSMA_35-cPFC_35, cSMA_35-aPFC_35) were performed in order to study TIB performance differences in the whole- body balance task (DBT) between groups on the first training day (TD1). If necessary, data was corrected for sphericity using Greenhouse-Geisser correction. In order to compare tDCS effects on TD2, we computed the difference between trial 1 on TD2 with trial 15 on TD1 and compared these values across groups using an univariate ANOVA. Subsequently, ANOVA$_{RM}$ with factor TIME was performed to investigate the TIB performance on TD2 within groups. To compare TIB performance between groups, an ANOVA$_{RM}$ with factor TIME and GROUP was performed. To compare TIB performance during aSMA_35-cPFC_50 with the other tDCS conditions, we performed separate ANOVA$_{RM}$ with factor TIME and GROUP.

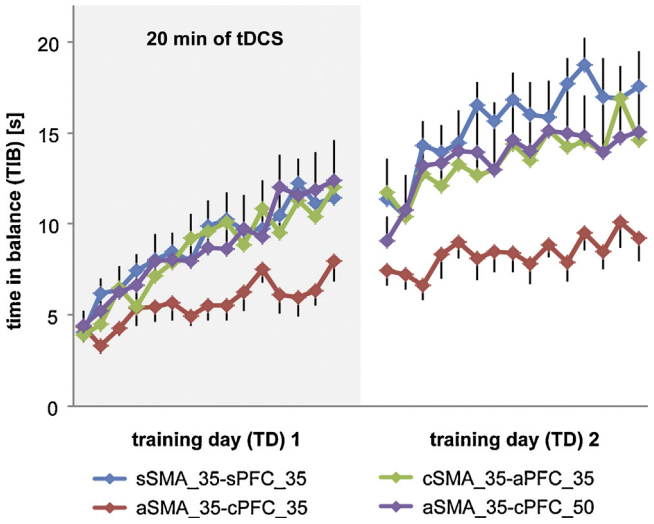

Fig. 2. Behavioural results. On the first training day (TD 1), anodal tDCS over SMA with an electrode (cathode) placed over the right PFC (aSMA_35-cPFC_35) impaired motor skill learning of the DBT compared to sham. This effect was still present on the second day of training (TD 2). Reversing the polarity (cSMA_35-aPFC_35) did not affect motor skill learning neither on TD 1 nor on TD 2. Application of anodal tDCS over SMA together with a larger, presumably more ineffective tDCS electrode (cathode) over the right PFC (aSMA_35-cPFC_50) did not affect the outcome of DBT learning. In fact, due to the electrode size, this observed effect cannot be attributed exclusively to SMA stimulation.

3. Results

There was no significant difference in attention (pre: univariate ANOVA, $F_{(2,27)} = 0.64$, $p = 0.54$, post: univariate ANOVA, $F_{(2,27)} = 0.59$, $p = 0.56$), fatigue (pre: univariate ANOVA, $F_{(2,27)} = 0.00$, $p = 1$, post: univariate ANOVA, $F_{(2,27)} = 0.59$, $p = 0.56$) or discomfort (pre: univariate ANOVA, $F_{(2,27)} = 0.00$, $p = 1$, post: univariate ANOVA, $F_{(2,27)} = 1.6$, $p = 0.22$) between groups.

3.1. Online-effects of tDCS on complex motor skill learning (TD1)

DBT performance on the first trial (trial1) did not differ between groups (sSMA_35-sPFC_35 aSMA_35-cPFC_35, cSMA_35-aPFC_35; univariate ANOVA, $F_{(2,27)} = 0.153$, $p = 0.859$). However, an ANOVA$_{RM}$ with factor TIME × GROUP revealed a significant interaction ($F_{(10.07,\ 135.91)} = 2.39$, $p = 0.012$), indicating a difference in complex motor skill learning in at least one of the experimental groups tested (please see Fig. 2). Time in balance (TIB) increased from 4.02 ± 0.5 s (mean ± SEM) in the initial trial to 11.41 ± 1.5 s in the last trial (trial 15) for sSMA_35-sPFC_35 (ANOVA$_{RM}$ with factor time (trial1-15), $F_{(14,\ 126)} = 13.52$, $p < 0.0001$). For cSMA_35-aPFC_35, TIB increased from 3.87 ± 0.5 s to 12.02 ± 1.6 s (ANOVA$_{RM}$, $F_{(14,126)} = 9.6$, $p < 0.0001$). On the other hand, TIB for aSMA_35-cPFC_35 was less pronounced as compared to sham since individual performance in the DBT increased from 4.36 ± 0.8 s in the initial trial to only 7.92 ± 1.1 s in the last trial (ANOVA$_{RM}$, $F_{(14,126)} = 5.43$, $p = 0.001$). Comparing TIB performance between sSMA_35-sPFC_35 and aSMA_35-cPFC_35 revealed a significant interaction (ANOVA$_{RM}$ with factor TIME (trial 1-15) and GROUP (sSMA_35-sPFC_35, aSMA_35-cPFC_35) ($F_{(5.74,103.3)} = 3.87$, $p = 0.006$, corrected for multiple comparisons, Fig. 2)). On the other hand, no such interaction could be observed when comparing cSMA_35-aPFC_35 with sSMA_35-sPFC_35 ($F_{(4.52,\ 81.39)} = 0.82$, $p = 0.53$).

3.2. Reversibility of tDCS effects on the second training day (TD2)

On the second day of DBT training (TD2 without tDCS), TIB in the aSMA_35-cPFC_35 group was still impaired as compared to sham stimulation (comparison trial1 on TD2, two samples *T*-Test: $p = 0.032$, Fig. 2). However, comparing TIB of trial15 on TD1 vs. trial1 on TD2 within groups revealed no significant differences (univariate ANOVA, $F_{(2,27)} = 0.08$, $p = 0.92$), indicating a successful consolidation of the newly acquired motor skills. Comparing DBT performance on TD2 revealed a main effect of GROUP ($F_{(2,27)} = 10.42$, $p < 0.0001$) while the TIME × GROUP interaction was not significant ($F_{(14.71,\ 198.59)} = 1.52$, $p = 0.102$). More specifically, while subjects in the sSMA_35-sPFC_35 and cSMA_35-aPFC_35 group significantly improved TIB on TD2 (s-tDCSSMA: $F_{(14,126)} = 5.63, p < 0.0001$; c-tDCSSMA: $F_{(14,126)} = 2.82, p = 0.001$), the improvement for aSMA_35-cPFC_35 was less pronounced but still significant ($F_{(14,126)} = 1.86$, $p = 0.037$).

3.3. Effect of PFC stimulation on complex motor skill learning

To disentangle whether the impaired motor skill learning for aSMA_35-cPFC_35 was due to a modulation of SMA or PFC, we performed an additional control experiment (Fig. 1B). Here, we applied tDCS (anode) over SMA together with a larger, more ineffective electrode (cathode) over the right PFC (aSMA_35-cPFC_50). Comparing DBT performance of aSMA_35-cPFC_50 with aSMA_35-cPFC_35 on TD1 revealed a significant TIME × GROUP interaction ($F_{(3.52,\ 59.89)} = 3.15$, $p = 0.025$), indicating a differential amount of TIB improvement across groups (Fig. 2). TIB for aSMA_35-cPFC_50 improved from 4.39 ± 0.9 s in the initial trial of TD1 to 12.38 ± 2.2 s (trial15). Comparing TIB performance of aSMA_35-cPFC_50 with sham or cSMA_35-aPFC_35 revealed no significant difference (TIME × GROUP interaction aSMA_35-cPFC_50 vs. sham: $F_{(3,9,66.25)} = 0.68$, $p = 0.6$; TIME × GROUP interaction aSMA_35-cPFC_50 vs. cSMA_35-aPFC_35: $F_{(3.29,\ 55.91)} = 0.98$, $p = 0.42$), indicating that the amount of motor skill learning did not differ between these groups.

Comparing TIB on TD2 (without tDCS application) revealed a significant TIME × GROUP interaction when comparing aSMA_35-cPFC_50 with aSMA_35-cPFC_35 ($F_{(14,28)} = 1.77$, $p = 0.044$), indicating a differential amount of TIB improvement over time. No such interaction could be observed when comparing aSMA_35-cPFC_50 with sham or cSMA_35-aPFC_35 ($p \geq 0.4$ for all comparisons). These results indicate that TIB performance improvements did not differ between aSMA_35-cPFC_50 and sham or cSMA_35-aPFC_35. In summary, the results on TD1 provide novel evidence that (A) SMA stimulation on TD1 did not affect DBT learning and (B) that the tDCS electrode (35 cm^2) over the right PFC seems to deteriorate TIB performance of the DBT since a larger (50 cm^2) tDCS electrode (cathode) together with a 35 cm^2 tDCS electrode over SMA (anode) did not affect DBT learning.

4. Discussion

In the present study, we investigated online and offline effects of tDCS over SMA on complex multi-joint motor skill learning. Anodal tDCS over SMA with an electrode (cathode) placed over the right PFC impaired motor skill learning of the DBT compared to sham. This effect was still present on the second day of training. Reversing the polarity (cathode over SMA, anode over right PFC) did not affect motor skill learning neither on the first nor on the second day of training. To better disentangle whether the impaired motor skill learning was due to a modulation of SMA and/or PFC, we performed an additional control experiment. Interestingly, this alternative tDCS electrode setup (large tDCS electrode over PFC, cathode) did not affect the outcome of DBT learning relative to sham. Our results provide novel evidence that a modulation of the (right) PFC by the 35 cm^2 cathodal tDCS electrode seems to impair complex multi-joint motor skill learning. We suggest that inhibition of higher cognitive processes such as strategy finding and/or feedback processing during initial stages of complex skill learning rather than excitation of SMA might explain our findings. Hence, future studies should take the positioning not only of the "target" but also of the second tDCS electrode into account when investigating complex motor skill learning. In fact, based on our findings in complex motor skill learning, the terminology of the so-called tDCS "reference" electrode should preferentially only be used in an extracephalic montage [26] or when very large tDCS electrodes ($\sim$100 cm^2) are used [27].

A general assumption for simplified models of motor skill learning is that application of anodal tDCS [3] can facilitate motor learning by an up-regulation of cortical excitability within M1. For example, it has been shown that subjects performed better in a serial reaction time task [4], showed increased visuo-motor learning [6] or an enhanced motor function in the non-dominant hand [12] when combining motor practice and anodal tDCS over M1. Likewise it has been assumed for cathodal tDCS that down-regulation of excitability within M1 results in impaired motor skill learning. However, recent studies indicate that this polarity-specific change must not necessarily be true. While some studies showed inhibitory effects of cathodal tDCS on motor learning processes [11], others did not find any influence on sequence learning tasks [4,10].

Such afore mentioned assumptions must not necessary apply to more complex motor behaviour and/or learning. We suggest that (A) tDCS-effects on a behavioural level are highly dependent on task complexity and that (B) the tDCS electrode placement over the contralateral forehead (PFC) might play a crucial role when investigating complex motor skill learning.

For simplified models of motor skill learning such as hand movements with sequential character, no study reported any influence of tDCS electrodes when placed over the contralateral forehead (for review see [1]). However, the DBT used in the present study is certainly a more complex task than previously used motor skill learning paradigms since (A) over the time course of learning subjects had to develop an individual strategy of coordinated whole body movements to perform the task and (B) whole body balancing requires the simultaneous processing of multimodal (e.g. visual, vestibular and proprioceptive) information and its conversion into appropriate motor commands. In addition, cognitive factors during learning might play an important role in the DBT, to allow for economical and targeted compensatory movements of the upper and lower extremities or the trunk. Hence, it is reasonable to assume that in our paradigm, down-regulation of information processing in prefrontal brain regions in early stages of motor skill learning by means of tDCS (cathodal PFC stimulation) might have an influential role as well.

The majority of recent motor learning studies focused on an application of tDCS over M1, whereas little is known about tDCS-effects in other motor-related brain regions outside M1. Recently, it has been shown that SMA but not pre-SMA facilitates short-term visuomotor learning [6]. In our study, a modulation of SMA did not influence complex motor skill learning. The SMA is linked to planning and preparation of future motor acts as well as to inhibition and repetition of motor actions [18,20,21,28,29]. It seems reasonable to assume that a successful execution of a motor plan depends on an exact representation of the desired motor action. In the present study, subjects performed the DBT for the first time, without having any prior representations of neither a motor plan nor strategies to optimize task performance. Hence, our study design can obviously not address the question whether

stimulation of SMA during later stages of motor skill learning would facilitate TIB performance. Indeed, some studies found a greater activation of SMA during later stages of motor skill learning as compared to early stages [29–32]. Thus, one can assume that SMA is less involved in the initial learning period in DBT but is stronger involved when movements become self-initiated and guided by internal cues [33–35]. In fact, Taubert et al. found structural and functional brain alterations in SMA after two weeks of DBT training [23]. In support of this, Hamzei and colleagues recently found a positive correlation between functional connectivity in SMA and the number of training sessions of short motor skill training [36].

Our study bears some potential limitations: Due to the limited spatial resolution of this particular brain stimulation technique, it is reasonable to assume that we did not exclusively stimulated SMA. In fact, a modulation of adjacent cortical areas such as pre-SMA might also have affected the amount of motor skill learning. Apart from stimulating SMA, it would also be of interest for future studies to stimulate other task-related brain regions such as the primary motor cortex (M1) or the cerebellum. Finally, it would be interesting to disentangle whether left prefrontal stimulation would yield similar inhibitory effects on complex whole body motor skill learning.

In summary, we suggest that the effects of tDCS on motor skill learning are highly dependent on task complexity and that future studies should take the positioning of *both* tDCS electrodes into account when investigating complex motor skill learning.

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