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Probing for hemispheric specialization for motor skill learning: a transcranial direct current stimulation study

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¹Human Cortical Physiology and Stroke Neurorehabilitation Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; ²Motor Performance Laboratory, Neurological Institute, Columbia University, New York, New York; ³Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland; ⁴Department of Neurology, Albert-Ludwigs-University, Freiburg, Germany; and ⁵Departments of Neurology and Neuroscience, Johns Hopkins University, Baltimore, Maryland

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Schambra HM, Abe M, Luckenbaugh DA, Reis J, Krakauer JW, Cohen LG. Probing for hemispheric specialization for motor skill learning: a transcranial direct current stimulation study. *J Neurophysiol* 106: 652–661, 2011. First published May 25, 2011; doi:10.1152/jn.00210.2011.—Convergent findings point to a left-sided specialization for the representation of learned actions in right-handed humans, but it is unknown whether analogous hemispheric specialization exists for motor skill learning. In the present study, we explored this question by comparing the effects of anodal transcranial direct current stimulation (tDCS) over either left or right motor cortex (M1) on motor skill learning in either hand, using a tDCS montage to better isolate stimulation to one hemisphere. Results were compared with those previously found with a montage more commonly used in the field. Six groups trained for three sessions on a visually guided sequential pinch force modulation task with their right or left hand and received right M1, left M1, or sham tDCS. A linear mixed-model analysis for motor skill showed a significant main effect for stimulation group (left M1, right M1, sham) but not for hand (right, left) or their interaction. Left M1 tDCS induced significantly greater skill learning than sham when hand data were combined, a result consistent not only with the hypothesized left hemisphere specialization for motor skill learning but also with possible increased left M1 responsiveness to tDCS. The unihemispheric montage effect size was one-half that of the more common montage, and subsequent power analysis indicated that 75 subjects per group would be needed to detect differences seen with only 12 subjects with the customary bihemispheric montage.

motor cortex; neurorehabilitation; neuromodulation; brain stimulation

IN RIGHT-HANDED INDIVIDUALS, cerebral specialization for various cognitive functions has long been recognized, from the superior visuospatial information processing of the right hemisphere to the language processing of the left (for example, see Geschwind 1965; Hugdahl and Davidson 2003). In the motor domain, studies in patients have shown that injury to left hemisphere motor areas more commonly results in apraxia than right hemisphere injury (Haaland et al. 2000; Zwinkels et al. 2004), suggesting a left-sided specialization for the ability to recall and perform previously learned purposeful movements (see historical reviews, Goldenberg 2003; Pearce 2009). It is

unclear, however, if analogous specialization exists for motor skill learning, the practice-dependent improvement in task performance (Reis et al. 2009).

A role for the left hemisphere in praxis has been suggested by various methodologies consistently showing more left than right hemisphere activity when the ipsilateral left hand is engaged in complex movements. In young, healthy right-handers, functional imaging studies show pronounced activation of left-sided primary motor (M1) and secondary motor (e.g., premotor, supplementary motor, and parietal) cortical areas during performance by either hand on various motor tasks (Hayashi et al. 2008; Kawashima et al. 1993; Kim et al. 1993; Kobayashi et al. 2003; Mattay et al. 1998; Nirrko et al. 2001; Singh et al. 1998; van Mier et al. 1998; Verstynen et al. 2005). Similarly, left more than right motor areas are more active during tool use imagery (Moll et al. 2000), planning (Bohlhalter et al. 2009; Johnson-Frey et al. 2005; Kroliczak and Frey 2009), and pantomiming (Choi et al. 2001; Hermsdorfer et al. 2007; Johnson-Frey et al. 2005; Moll et al. 2000; Ohgami et al. 2004) by either hand, even when controlling for processing of linguistic stimuli (Kroliczak and Frey 2009). Transcranial magnetic stimulation (TMS) studies demonstrate strong M1 excitability increases with contralateral (e.g., Datta et al. 1989; Hess et al. 1986) and ipsilateral hand movement (Hess et al. 1986; Lee et al. 2010; Liang et al. 2008; Muellbacher et al. 2000; Perez and Cohen 2009b; Stedman et al. 1998; Tinazzi and Zanette 1998; Woldag et al. 2004), with greater left M1 than right M1 excitability increases during ipsilateral hand movement (Ghacibeh et al. 2007; Ziemann and Hallett 2001). Along these lines, EEG during sequential finger movements and inverted mirror drawing shows increased left hemisphere cortical processing during performance by either hand, but increased right hemisphere processing with left hand performance alone (Bai et al. 2005; Serrien and Spape 2009). Collectively, these data suggest that the left hemisphere is involved in some way when either hand is performing a complex motor task. It could be conjectured that the left hemisphere has a capacity for motor control not possessed by the right hemisphere and that this specialization could extend to motor learning.

The studies in healthy subjects and patients described above provide evidence for a left hemisphere role in praxis and raise the question of whether the left hemisphere is specialized for motor learning. We are defining specialization in a way anal-

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ogous to how it has been defined for lesion-based studies in motor control (Schaefer et al. 2009): namely, a hemisphere is specialized for a particular function if lesioning it diminishes that function in both limbs and the impairment in that function is greater in the ipsilesional limb than if the nonspecialized hemisphere were lesioned. Thus, in the case of augmenting function, stimulating the specialized hemisphere should result in greater augmentation of behavior in both limbs compared with stimulating the other hemisphere.

Surprisingly, there have been few studies in this area in the motor system. Healthy young subjects learning the serial reaction time task (SRTT) with the left hand show increased activation in left M1, left premotor, and supplementary motor areas (Grafton et al. 2002), similar to activation patterns seen when the right hand learns the same task (Grafton et al. 1995). Importantly, however, imaging and neurophysiology studies alone cannot prove greater left hemispheric specialization for motor learning, because left hemispheric activity could be redundant or even epiphenomenal. Attempts to prove specialization require virtual lesion or enhancement approaches in healthy subjects or lesion studies in patients.

In one study that compared patients with stroke in the left or right hemisphere, patients with left hemisphere stroke took two to three times longer to learn a sequence of three hand movements made with either hand, ostensibly despite comparable hand strength and function (Kimura 1977). A single virtual lesion study using repetitive transcranial magnetic stimulation (rTMS) at 1 Hz found improved early acquisition of a sequencing task with the left hand after left M1 rTMS, with a subsequent learning rate parallel to that of sham rTMS (Kobayashi et al. 2009). rTMS at 1 Hz is known to reduce stimulated M1 excitability (for example, see Chen et al. 1997) while increasing unstimulated M1 excitability (Gilio et al. 2003; Heide et al. 2006; Kobayashi et al. 2004; Schambra et al. 2003), making the source of the behavioral effects more difficult to pinpoint.

In the present study, we used an enhancement-of-function approach, employing anodal transcranial direct current stimulation (tDCS) to infer the innate functional role of the stimulated hemisphere. When applied to the M1, anodal tDCS increases motor cortical excitability (Nitsche and Paulus 2000), facilitates motor performance (Antal et al. 2004b; Boggio et al. 2006; Hummel et al. 2009; Nitsche et al. 2003), and potentiates formation of motor memories (Galea and Celnik 2009) and learning of motor skill in the opposite hand (Fritsch et al. 2010; Reis et al. 2009), with possible ipsilateral effects as well (Vines et al. 2006, 2008). Excitability changes in the unstimulated M1 have not been reported so far with anodal tDCS. Our core assumption in using anodal tDCS was that if motor learning is enhanced when the M1 is stimulated, then this area and possibly interconnected regions contribute to motor learning in the absence of stimulation.

Nearly all stimulation studies to date in the motor system have utilized a bihemispheric tDCS montage (i.e., the anode placed over one M1 and the cathode over the opposite M1 or contralateral supraorbital region), which may lack the spatial focality needed to probe a single hemisphere (Datta et al. 2009; Sadleir et al. 2010; Wagner et al. 2007). We thus used a unihemispheric tDCS montage, with a cephalic M1 anode and an extracephalic shoulder cathode, in an effort to provide more focal stimulation as predicted by modeling (Wagner et al. 2007). This more focal montage has been shown to increase

motor cortical excitability (Cogiamanian et al. 2007; Moliadze et al. 2010), but its effects on motor skill learning are not known.

We first asked whether either hemisphere plays a role in motor skill learning in both hands, which would be indicated by augmented contralateral and ipsilateral hand learning by stimulation of that hemisphere. We then asked whether there is a specialized hemisphere for motor skill learning, which would be indicated by greater augmentation of learning in both hands by stimulation of one hemisphere. We evaluated motor skill learning in 93 healthy subjects receiving left M1 anodal, right M1 anodal, or sham unihemispheric tDCS during right or left hand training over multiple days.

Our two hypotheses were predicated on the assumption that left hemisphere stimulation augments skill in the right hand. Our first hypothesis was that relative to sham, left hemisphere stimulation would enhance learning in the left hand. Our second hypothesis was that relative to right hemisphere stimulation, left hemisphere stimulation would cause more skill enhancement in the left hand. Proving the first hypothesis would imply that the left hemisphere is able to influence motor learning in the left hand. Proving the second hypothesis would imply a left hemisphere specialization for skill learning. The magnitude of the behavioral effect with unihemispheric stimulation was also compared with the behavioral effect found in a previous study using bihemispheric stimulation (Reis et al. 2009).

MATERIALS AND METHODS

Subjects. Ninety-three right-handed adults (47 M, 46 F; mean age 27.8 ± 0.6 yr) were studied. All subjects gave written informed consent to participate in this National Institute of Neurological Disorders and Stroke (NINDS) Institutional Review Board-approved study, in accordance with the Declaration of Helsinki. All experiments were carried out in the Human Cortical Physiology and Stroke Neurorehabilitation Section (NINDS, NIH). Inclusion in the study required normal general and neurological examinations; right-hand dominance; a lack of chronic neurological, psychiatric, or medical conditions; and a lack of psychoactive medication use.

Groups. Six groups of subjects were studied in a factorial design. Three groups trained with the right hand, and three groups trained with the left hand. Each of the three groups for a given hand received left M1, right M1, or sham stimulation. In the right-hand training groups, 16 subjects per group received either left or right M1 stimulation, and 15 subjects received sham stimulation. In the left-hand training groups, 16 subjects received right M1 stimulation, and 15 subjects per group received either left M1 or sham stimulation.

Task. All subjects trained on the Sequential Visual Isometric Pinch Task (SVIPT). The SVIPT paradigm has been described previously (Reis et al. 2009). Briefly, subjects squeezed a force transducer between index finger and thumb to move a cursor on a computer screen through an array of five horizontal targets (Fig. 1A), with each target requiring a different pinch force. The force requirements across the horizontal space increased logarithmically, with the maximal force requiring $\sim 30\%$ maximal voluntary contraction. Target order was numbered above the targets and did not vary between subjects or across sessions. Subjects were instructed to move the cursor as quickly and as accurately as possible through the target array. Movement time was measured from movement onset to reaching *target 5* and was taken as the mean of a 10-trial bin. Error rate was the proportion of trials with at least one target over- or undershoot in a 10-trial bin. Skill was defined as the combination of these variables, using the following mathematical model fitting the speed-accuracy trade-off curve for the SVIPT (Reis et al. 2009):

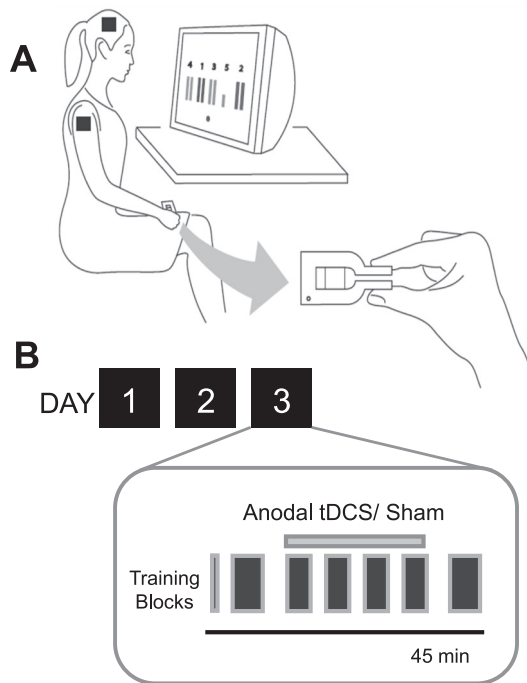


Fig. 1. Methods. *A*: experimental setup: 6 parallel groups trained on the sequential visual isometric pinch task (SVIPT), using a force transducer held between thumb and index finger. During training, subjects received either anodal or sham direct current stimulation (tDCS; black squares) in a unihemispheric montage, with the anodal electrode placed over the motor cortex (M1) and the cathodal electrode placed over the ipsilateral deltoid muscle. *B*: daily training paradigm: subjects trained for 3 consecutive days on the SVIPT, with 3 warm-up trials and 200 daily trials divided into 6 blocks lasting ~45 min. The middle 4 blocks had 30 trials, and the first and last blocks had 40 trials. Anodal or sham tDCS was given for 20 min during the middle 4 blocks on each day.

$$\text{skill} = \frac{1 - \text{error rate}}{\text{error rate} [\ln(\text{movement time})^{5.424}]}$$

This model was validated for our investigation in two separate groups of right-handed subjects (not included in subsequent analysis) trained under our experimental paradigm with their right or left hand (Fig. 2). Use of this model enabled us to avoid mistaking a move along the speed-accuracy trade-off curve (e.g., reduced movement time with increased error rate) as an actual skill gain. Thus an improved relationship between speed and accuracy (e.g., a reduced movement time with a reduced or stable error rate, or vice versa) was reflected as an increased skill, consistent with previous work (Fritsch et al. 2010; Reis et al. 2009).

This task was developed to assess skill rather than adaptation. Whereas adaptation allows the motor system to return to normal levels of performance in the setting of a perturbation, motor skill is the acquisition of a higher level of performance with repeated practice (Hallett et al. 1996; Shadmehr and Wise 2005). One view of this difference is that adaptation is mediated through changes in a forward model, whereas skill develops as a slower process of acquiring an optimal feedback control (Shadmehr and Krakauer 2008). We consider the SVIPT a motor skill task because subjects improve movement execution, i.e., shift their speed-accuracy trade-off relationship with practice (Reis et al. 2009), which also can be inferred to be happening in sequential finger tapping tasks (Karni et al. 1995, 1998) but less so in adaptation tasks or the SRTT (Robertson 2007). This distinction between improved execution versus other forms of procedural learning is particularly important, because they may be mediated by separate neural substrates (Hallett et al. 1996). Finger-

tapping skill is associated with learning-related activation in contralateral M1 (Karni et al. 1995, 1998), whereas the SRTT is associated with activations in dorsolateral prefrontal cortex and mediotemporal lobe (Schendan et al. 2003; Willingham et al. 2002), and adaptation is associated with activations in posterior parietal cortex and cerebellum (Diedrichsen et al. 2005; Ghilardi et al. 2000; Krakauer et al. 2004).

Stimulation. We used two 25-cm² electrodes soaked in tap water to apply tDCS (Iomed Phoresor II PM850 device; Chattanooga Group) in a unihemispheric montage (Cogiamanian et al. 2007) to reduce potential influences of current spreading over both hemispheres (Datta et al. 2009; Sadleir et al. 2010; Wagner et al. 2007). The first dorsal interosseus hotspot was localized in all subjects with TMS (Magstim 200²; Magstim) on the first day, and the scalp was re-marked daily with ink to ensure a spatially consistent electrode placement. The anodal electrode was centered over the target M1 hotspot. For convenience, we refer to it here as the “M1” electrode, although stimulation of adjacent areas could not be completely ruled out with the size of electrodes used (see Fig. 2 in Reis et al. 2009). The cathodal electrode was placed over the ipsilateral deltoid to avoid currents flowing to the opposite hemisphere (Wagner et al. 2007) (Fig. 1A). Because we gave only anodal or sham stimulation to the M1, any

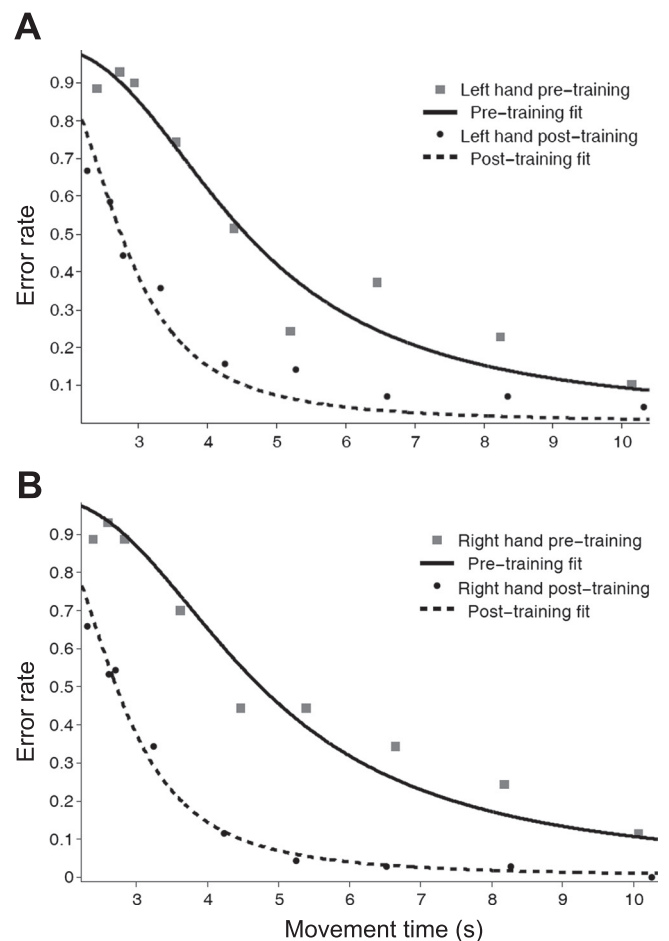


Fig. 2. Validation of the speed-accuracy trade-off mathematical model for both hands. We confirmed that the previously modeled speed-accuracy trade-off function was also appropriate for use in this study. Two independent groups of 7 right-handed subjects trained for 3 days with either their left (*A*; 4 M, 3 F, age 30 ± 3.2 yr) or right hand (*B*; 3 M, 4 F, age 28.6 ± 2.1 yr). Stimulation was not given. A metronome paced subjects to move at different speeds, and average movement times and error rates were recorded. We fit the following previously derived speed-accuracy function (Reis et al. 2009) to the pre- and posttraining data. We found adjusted R-squares pre- and posttraining values of 0.94 and 0.94, respectively, for the left hand and 0.95 and 0.98, respectively, for the right.

Table 1. Demographic and psychophysical data

Group	<i>n</i>	Sex, M:F	Age, yr	Handedness ^a	Sleep Duration, h	Sleepiness ^b	Attention ^c	Hand Fatigue ^d	Placebo ^e	Motivation ^f
Left hand										
Sham	14	7:7	26.5 ± 1.2	90.3 ± 2.5	7.1 ± 0.2	8.4 ± 0.4	6.9 ± 0.4	6.5 ± 0.4	6.3 ± 1.6	7.0 ± 0.4
Left M1	15	8:7	25.4 ± 0.7	94.9 ± 2.0	7.0 ± 0.2	7.7 ± 0.3	6.7 ± 0.4	6.7 ± 0.4	5.4 ± 0.4	7.0 ± 0.4
Right M1	15	6:9	29.6 ± 2.5	90.7 ± 3.8	7.1 ± 0.2	8.0 ± 0.4	7.0 ± 0.2	6.7 ± 0.3	6.1 ± 0.3	7.1 ± 0.4
Right hand										
Sham	14	7:7	29.0 ± 1.7	92.1 ± 5.5	7.1 ± 0.2	8.4 ± 0.3	7.1 ± 0.2	6.7 ± 0.5	5.9 ± 0.3	7.7 ± 0.4
Left M1	14	7:7	27.1 ± 1.3	96.1 ± 2.5	7.1 ± 0.2	7.3 ± 0.3	6.8 ± 0.4	6.6 ± 0.4	5.8 ± 0.2	7.1 ± 0.4
Right M1	15	8:7	28.9 ± 1.1	93.4 ± 2.8	6.9 ± 0.1	7.9 ± 0.4	6.6 ± 0.4	6.5 ± 0.4	5.9 ± 0.3	7.6 ± 0.5
<i>P</i> value ^g		0.98	0.11	0.80	0.94	0.99	0.90	0.21	0.97	0.75

Data are mean ± SE; *n* = no. of subjects. ^aHandedness: Edinburgh handedness scale, where a score of 100 is completely right-hand dominant. All psychophysical scales were scored 0–10. ^bSleepiness: 0 = falling asleep, 10 = wide awake. ^cAttention: 0 = highly distracted, 10 = highly focused. ^dHand fatigue: 0 = hand exhausted, 10 = hand not at all tired. ^ePlacebo: 0 = stimulation will hurt performance, 5 = no expected effect, 10 = stimulation will help performance. ^fMotivation: 0 = not excited to participate, 10 = highly excited to participate. ^g*P* value: group means were compared with a 1-way ANOVA, except for the χ^2 assessment of sex distribution.

reference hereafter to “tDCS” refers to anodal tDCS. tDCS (1 mA) was delivered for 20 min (current density 0.04 mA/cm²; total charge 0.048 C/cm² per electrode) during training. Sham tDCS was given by ramping the stimulator up and down over ~15 s at the beginning of the 20-min period (Gandiga et al. 2006). Subjects were blinded to the type of stimulation they received. During all stimulation sessions, subjects were repeatedly asked about any potential side effects (e.g., headache, skin discomfort, inattention, sleepiness).

Training paradigm. Subjects participated in three consecutive daily training sessions at the same time each day (Fig. 1B). On the first training session, subjects observed three demonstration trials of the SVIPT and then practiced three trials. Subjects warmed up with three trials on the second and third training days. Subjects trained 200 trials broken into 6 blocks, with anodal or sham tDCS given daily during the middle 120 trials (4 blocks). The first and last blocks were 40 trials apiece, and the middle 4 blocks were 30 trials apiece. Subjects had ~30 s rest between each block. The primary outcome measures were the baseline skill on *day 1* (mean skill of the first 10 trials of *block 1*) and the final skill on *day 3* (mean skill of the last 10 trials of *block 6*).

Psychophysical information. Before training, subjects gave daily self-reports of sleep duration, attention, hand tiredness, general fatigue, anticipation of benefit from stimulation (placebo effect), and motivation to participate. Degree of handedness was assessed by Edinburgh Handedness Inventory (Oldfield 1971).

Statistical analysis. Of the 93 subjects initially enrolled in the study, 87 were included in the final analysis and this report. One subject per group was excluded due to a final skill greater than two standard deviations above the group mean to reduce within-group variability. A linear mixed model with restricted maximum likelihood estimation, rather than logarithmic transformation of the data as in our previous report (Reis et al. 2009), was used to control for heteroscedasticity. We evaluated skill over time (baseline, final), by stimulation group (left M1 tDCS, right M1 tDCS, and sham tDCS), and by hand (right, left) in a full-factorial fixed-effects model. Schwarz’s Bayesian criteria were used to determine the best-fitting variance-covariance structure, which was diagonal. Bonferroni post hoc tests were used to examine interactions and omnibus main effects. A repeated-measures ANOVA with Bonferroni correction was used to examine effects of stimulation group on movement time and error rate. To assess the comparative magnitude of the experimental effect on the final skill of each group, effect sizes were calculated by doubling the uncorrected post hoc *t*-statistic and dividing that quantity by the square root of the degrees of freedom (Rosenthal 1994). By convention, an effect size (Cohen’s *d*) of 0.2 is small, 0.5 is moderate, and >0.8 is large (Cohen 1992). For demographic and psychophysical data, Pearson’s χ^2 test was used for a comparison of sex distributions, and a one-way ANOVA was used to compare the means of psychophysical assessments between groups. Significance was evaluated at *P* < 0.05,

two-tailed. All post hoc values are reported following correction for multiple comparisons. All data are means ± SE.

RESULTS

Mean age and sex in all six groups were comparable [$F_{5,81} = 1.9$, $P = 0.11$, and $\chi^2(5, n = 87) = 0.72$, $P = 0.98$, respectively], as was the Edinburgh Handedness Inventory score ($F_{5,81} = 0.47$, $P = 0.80$; Table 1). Self-reports of sleep duration, attention, hand tiredness, general fatigue, anticipation of benefit (placebo effect), and motivation to participate were also comparable (Table 1). Mild itching underneath either electrode was the only reported side effect but was comparably felt across groups.

We evaluated the effect of anodal (left M1, right M1) and sham tDCS on motor skill learning by either hand. There was no main effect of hand ($F_{1,85} = 0.39$, $P = 0.53$). There was a significant effect of stimulation group ($F_{2,85} = 3.47$, $P = 0.036$) and time ($F_{1,85} = 43.99$, $P < 0.001$) and a group × time interaction ($F_{2,85} = 4.48$, $P = 0.014$) on skill. The interaction indicates that skill was differentially modified over time depending on the group of stimulation, when hand data are combined (Fig. 3 and Table 2). Bonferroni post hoc tests

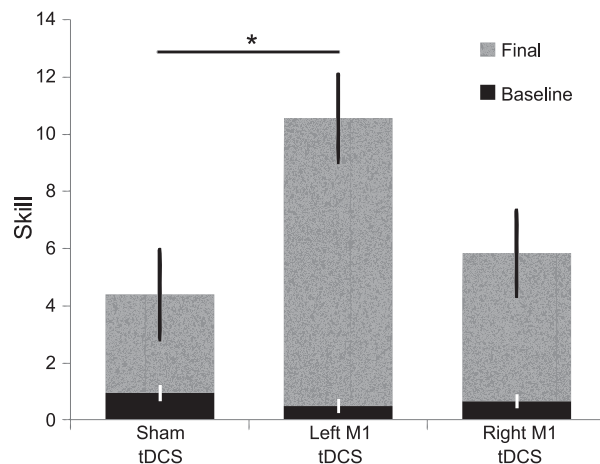


Fig. 3. Effect of stimulation group on skill. Baseline skills across groups were comparable. Left M1 stimulation significantly increased final skill compared with sham ($t_{81} = 2.71$, $P = 0.024$). Data are combined from the right and left hands and are mean (±SE) skill per stimulation group. Skill is the parameter that captures the change in the speed-accuracy trade-off function. **P* < 0.05.

Table 2. Baseline and final skills by stimulation group

Group	<i>n</i>	Baseline Skill	Final Skill	<i>P</i> Value
Sham	28	0.96 ± 0.25	4.38 ± 1.63	0.043
Left M1	29	0.50 ± 0.24	10.56 ± 1.60	>0.0001
Right M1	30	0.68 ± 0.24	5.83 ± 1.57	0.002

Data are means ± SE. *P* values of prepost contrasts are reported to demonstrate skill learning.

indicated no differences between the three stimulation groups at baseline. Left M1 stimulation resulted in higher final skill than sham ($t_{81} = 2.71$, $P = 0.024$; Fig. 3) and a nonsignificant trend for a difference with right M1 stimulation ($t_{81} = 2.11$, $P = 0.11$). Final skills with right M1 and sham stimulation were not significantly different ($t_{81} = 0.64$, $P = 1.00$). There was a significant group × time interaction for error rate ($F_{2,84} = 3.08$, $P = 0.05$) but not movement time ($F_{2,84} = 1.35$, $P = 0.26$; Fig. 4).

The interactions of hand × group ($F_{2,85} = 1.78$, $P = 0.18$), hand × time ($F_{1,85} = 0.12$, $P = 0.73$), and hand × group × time ($F_{2,85} = 1.14$, $P = 0.33$) on skill were nonsignificant (Fig. 5 and Table 3). Visual inspection of the hand-specific data for hypothesis-generating purposes reveals a trend for greater motor skill learning in both hands after training during left M1 tDCS, relative to right M1 or sham stimulation. Effect sizes describe these trends for future power calculations (Fig. 5).

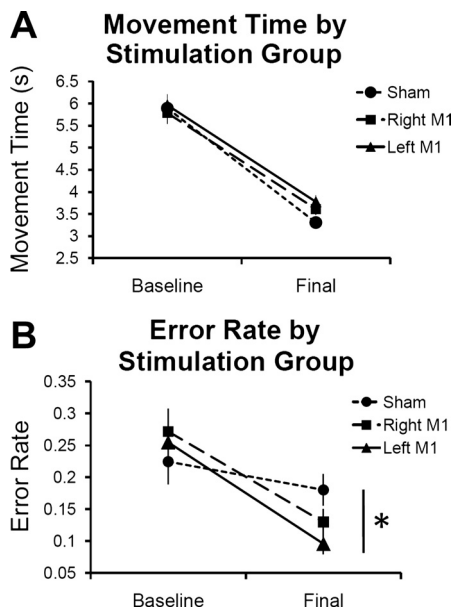


Fig. 4. Movement time and error rate changes across time by group of stimulation. A repeated-measures ANOVA was used to explore the effect over time of the stimulation group (left M1, right M1, or sham tDCS) on movement time and error rate in the combined hand data. *A*: for movement time, there was a significant effect of time ($F_{2,84} = 400.79$, $P < 0.001$), but the interaction group × time was nonsignificant ($F_{2,84} = 1.35$, $P = 0.26$). *B*: for error rate, there was a significant effect of time ($F_{1,84} = 31.9$, $P < 0.001$) and group × time interaction ($F_{2,84} = 3.08$, $P = 0.05$). Bonferroni post hoc tests showed no significant differences in error rate between the 3 stimulation groups at baseline or between the final error rate of the right M1 tDCS and sham stimulation groups. The final error rate of the left M1 tDCS group was significantly lower than that of the sham group ($t_2 = 2.93$, $P = 0.01$). These data underline the importance of using skill as the primary endpoint measure under the documented model to interpret opposing directional changes in movement variables (Reis et al. 2009).

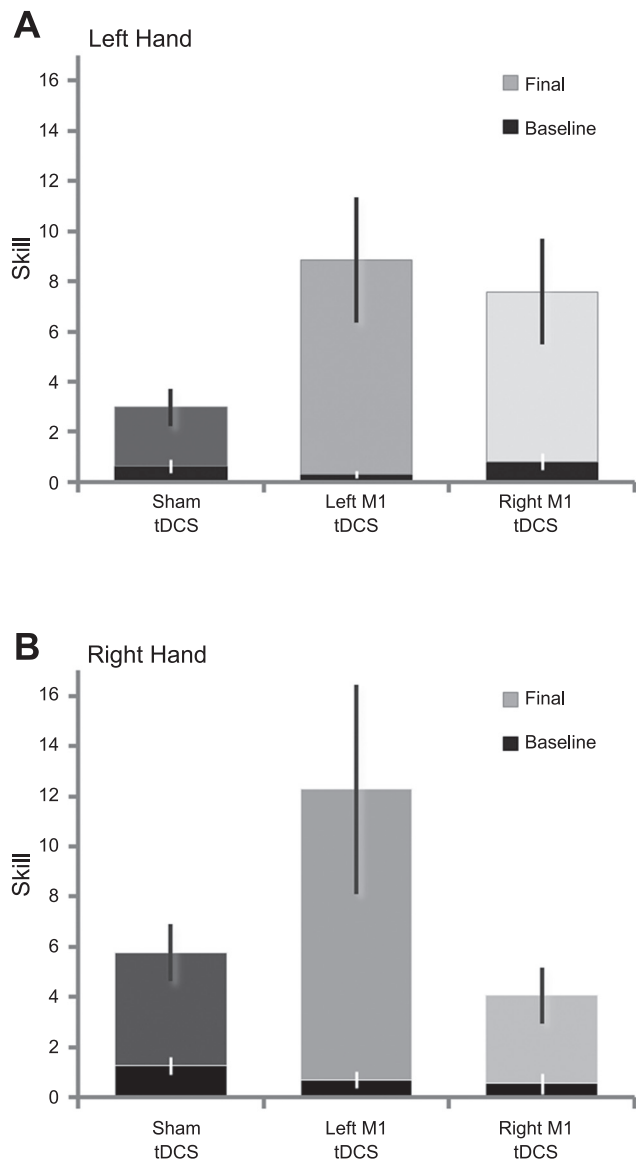


Fig. 5. Effects of tDCS on skill in each hand. Although group × time interactions were not significant in the left ($F_{2,42} = 2.51$, $P = 0.09$) or right hand ($F_{2,42} = 2.93$, $P = 0.06$), we ran within-hand post hoc *t*-tests to obtain descriptive information possibly useful for future power analyses. Within-hand baseline skills between groups were not significantly different. *A*: left hand: left M1 and right M1 tDCS induced final skills that were not significantly different from each other ($P = 1.00$) or from sham (LM1, $P = 0.21$; RM1, $P = 0.46$). *B*: right hand: left M1 tDCS induced relatively greater final skills than right M1 tDCS ($P = 0.037$) but not sham ($P = 0.15$). Right M1 tDCS induced final skills that were comparable to sham ($P = 1.00$). Data are mean (±SE) final skill. Final skill was used to determine stimulation effect size. Effect sizes: left LM1 tDCS relative to sham had moderate effects in the right ($d = 0.41$) and left hands ($d = 0.40$) hands. Right M1 tDCS relative to sham had a moderate effect in the left hand ($d = 0.35$) and a small negative effect in the right hand ($d = -0.07$). Left M1 relative to right M1 stimulation showed a moderate effect in the right hand ($d = 0.49$) but a small effect in the left hand ($d = 0.07$).

To ensure that minor variations in baseline skill did not impact final skill, we performed an additional linear mixed-model analysis using baseline skill as a covariate (Vickers 2001). Indeed, baseline skill did not correlate with final skill ($F_{1,81} = 0.44$, $P = 0.51$), and group ($F_{2,80} = 4.2$, $P = 0.021$), hand ($F_{1,80} = 0.18$, $P = 0.67$), and hand × group ($F_{2,80} = 1.29$, $P = 0.28$) interaction effects were comparable to the original analysis.

Table 3. *Baseline and final skills within hand*

Group	<i>n</i>	Baseline Skill	Final Skill	<i>P</i> Value
Left hand				
Sham	14	0.64 ± 0.27	2.97 ± 0.75	0.007
Left M1	15	0.30 ± 0.15	8.84 ± 2.50	0.002
Right M1	15	0.81 ± 0.32	7.58 ± 2.12	0.004
Right hand				
Sham	14	1.27 ± 0.53	5.78 ± 1.13	0.001
Left M1	14	0.71 ± 0.28	12.29 ± 4.17	0.01
Right M1	15	0.56 ± 0.41	4.07 ± 1.11	0.006

Data are mean ± SE. *P* values of prepost contrasts are reported to demonstrate skill learning.

To compare our results using the unihemispheric montage to those of a previous study using a bihemispheric montage and an otherwise identical paradigm (Reis et al. 2009), we used learning data from the right hand after left M1 anodal stimulation. Subject groups did not significantly differ in age, sex, educational level, or handedness. After 3 days of training with the right hand, bihemispheric tDCS induced a significantly greater final skill ($t_{21} = 2.14$, $P = 0.04$) relative to sham, whereas unihemispheric tDCS did not. Compared with sham, the effect size on final skill was large for bihemispheric tDCS ($d = 0.88$) and only moderate ($d = 0.41$) for unihemispheric tDCS. A power analysis (1-tailed *t*-test, $\alpha = 0.05$, $\beta = 0.2$) indicated that 75 subjects per group using the unihemispheric montage would be needed to detect the effect identified with only 12 subjects using the bihemispheric montage.

DISCUSSION

Our results demonstrate that left M1 stimulation with a unihemispheric tDCS montage induced greater motor learning than sham and a trend for a greater improvement than right M1 stimulation, when hand data were combined. Because unihemispheric tDCS enhanced skill less than bihemispheric tDCS, we were underpowered to detect possible differential effects of left M1, right M1, and sham tDCS on each hand. Nevertheless, these preliminary results (Fig. 3) suggest two alternative hypotheses: 1) left motor areas are specialized for motor learning in both hands, or 2) each hemisphere contributes equally well to motor skill learning in its contralateral hand, but left motor areas are more sensitive to cortical modulation by tDCS than the right ones.

How could the left hemisphere contribute to skill in the left hand? The possibility that the left hemisphere is specialized for skill learning in the left hand seems somewhat counter-intuitive, given that a large body of evidence indicates that motor execution is driven predominantly by the contralateral motor cortex: corticospinal tract lesions disrupt contralateral motor execution more than ipsilateral (Perez and Cohen 2009a; Porter and Lemon 1993), TMS of the M1 cortical hand area leads to robust contralateral hand muscle contractions (e.g., see Barker et al. 1985), and simple hand movement is associated with more predominant contralateral than ipsilateral motor area activation (Mattay et al. 1998; Verstynen et al. 2005). Thus, at the level of commands to muscles for skilled execution of a task, all evidence suggests that the motor commands emanate from contralateral motor areas. In addition, there is evidence suggesting that functional (Classen et al. 1999; Karni et al. 1995; Pascual-Leone et al.

1994; Zhuang et al. 1997) and structural plasticity (Kleim et al. 2002; Matsuzaka et al. 2007; Rioult-Pedotti et al. 1998) occurs in the motor cortex contralateral to the performing limb after motor training paradigms.

What, then, could the left hemisphere be contributing to the left hand during skill acquisition? Motor skill is likely made up of multiple cognitive components that can be considered in terms of a hierarchy of abstraction. Performing a specific motor task requires the specification of an action goal, selection of the right action to achieve that goal, and subsequent accurate execution of that action (Hoshi 2008; Yarrow et al. 2009). In the context of the SVIPT, a sequential movement task, subjects have to learn the relationship between cursor movements and required isometric forces, choose whether to be fast or cautious, specify the sequence of forces to apply, and then execute each force-producing movement element in the sequence with precision (Schmidt and Lee 2005). Either selecting or executing the accurate action more quickly could lead to a higher skill in our task. Thus it is possible that left hemisphere tDCS influenced some components of left hand skill acquisition more than others, an issue that requires future investigation. It should be noted that we did not have any *a priori* hypotheses with regard to potential differential hemispheric specializations for on-line effects, off-line effects, and retention, the components studied in our previous report (Reis et al. 2009). Our present goal was to first ascertain whether there was left hemisphere specialization overall, combining on-line and off-line effects. We did not investigate retention. In retrospect, it is clear that given the study's low power to detect even global learning differences, we would not have been able to look at learning subcomponents.

It is notable that the scant work suggesting left hemisphere specialization for motor skill has emphasized the learning of motor sequences (Grafton et al. 1995, 2002; Kimura 1977) rather than the quality of movement execution per se. Similarly, apraxia is a disorder of selecting purposeful action sequences involving tool use (e.g., Poizner et al. 1998; Rothi and Heilman 1997) rather than of motor execution; patients have minimal kinematic abnormalities when tool use is not required, such as with pointing or prehensile tasks under visual guidance (Ietswaart et al. 2006). A link between skill acquisition and praxis might therefore be the need for an explicit/semantic understanding of the motor task either before it can be learned or accessed after it has been learned (Krakauer and Shadmehr 2007). The present conjecture is that there may be an explicit/semantic component to both skill acquisition and retrieval. In acquisition of skills, it might be necessary to identify the task goal before it is possible to optimally combine and tune the individual movement elements that comprise the skill, whereas for a well-learned task, the explicit task goal must have access to the movement elements for their assembly into skilled performance. In support of this view is a recent study that showed that motor execution of sequence elements reached peak levels only after the full sequence was learned explicitly (Ghilardi et al. 2009). This also makes an interesting prediction that patients with apraxia may have difficulty learning a new skill task (Pistarini et al. 1991).

Asymmetry of response to stimulation. An alternative interpretation of the observed trends is that both hemispheres are equally active in motor skill learning for the contralateral hand but that the left M1 responds more robustly than the right M1

to anodal tDCS. Although previous data substantiated baseline differences in motor cortical excitability between hemispheres (Civardi et al. 2000; Ilic et al. 2004), to our knowledge no studies to date have directly compared the relative effects of anodal tDCS on left and right M1 excitability. The left M1 is anatomically larger than the right M1 and has a greater neuropil volume, suggestive of a greater synaptic profusion (Amunts et al. 1996, 2000; Foundas et al. 1998). By virtue of a larger pool of synapses, activity-associated modulation at the molecular level by anodal tDCS (Fritsch et al. 2010) may result in a more pronounced stimulation effect on the left. If anodal unihemispheric tDCS differentially modulates function due to differences in receptivity of the underlying cortex, one could expect to find greater motor skill learning with left M1 than right M1 stimulation, consistent with trends we saw. Mechanistic clarity could be gained by better powering future studies and by including an electrophysiological assay of M1 excitability changes.

The effect of stimulation montage on modulation of motor learning. A methodological comparison of unihemispheric tDCS was made with bihemispheric tDCS, to understand why a nonsignificant effect was seen even when an identical paradigm and similar groups sizes were used (Reis et al. 2009). We found that the effect size of unihemispheric stimulation in the right hand was about one-half that of bihemispheric stimulation.

Previous investigations using bihemispheric anodal tDCS (positioning 1 electrode over each cerebral hemisphere) have largely focused on the modulatory effects of M1 stimulation on hand motor function (Antal et al. 2004a; Boggio et al. 2006; Fritsch et al. 2010; Hummel et al. 2009; Nitsche et al. 2003; Reis et al. 2009; Vines et al. 2006, 2008). Some concerns raised about the bihemispheric tDCS montage have been the relative lack of focality and the likelihood that the reference electrode is not physiologically inert (Nitsche et al. 2008). Modeling studies have proposed that the use of a unihemispheric montage (with 1 electrode over a target cortical area and the second electrode over an extracephalic site, such as the shoulder) could lead to the more focal polarization of the hemisphere under the cephalic electrode (Wagner et al. 2007).

We employed an experimental design and behavioral task used successfully (Fritsch et al. 2010; Reis et al. 2009) and validated the skill measure model for our present experimental conditions (see Fig. 2). One main finding reported presently was the relatively reduced behavioral effect of the unihemispheric anodal tDCS montage. Compared with bihemispheric anodal tDCS, unihemispheric tDCS produced an effect size on skill acquisition that was approximately one-half. This diminished behavioral effect may have been due to differences in amount or location of charge density under the anode (Wagner et al. 2007). Our behavioral findings are consistent with a recent report indicating that unihemispheric tDCS causes a milder, more transient increase in motor cortical excitability compared with the bihemispheric montage (Moliadze et al. 2010). Interestingly, this reduced effect on neurophysiological excitability is overcome by doubling stimulation intensity, an appealing possibility to test behaviorally in future investigations. It is also conceivable that bihemispheric tDCS induces more sizable behavioral effects by stimulating more widespread regions of the cerebral cortex (Datta et al. 2009; Mi-

randa et al. 2006; Sadleir et al. 2010; Wagner et al. 2006) or by activating a more distributed cortical network (Lang et al. 2005; Stagg et al. 2009), either of which may enhance motor skill learning. One additional consideration is that the direction of the current flow induced by each montage (Wagner et al. 2007) might differentially affect distinct neuronal orientations and morphologies (Radman et al. 2009). Even with the unihemispheric montage, however, there is still a possibility that tDCS applied over M1 could influence activity in nearby regions such as dorsal premotor cortex or distant interconnected regions such as the supplementary motor area.

Finally, a power analysis of our data indicated that under our experimental conditions, a sixfold increase in subject number would have been required to detect the skill learning evident with bihemispheric tDCS. This finding underlines the need for a proper power calculation using best estimates of effect size before testing the behavioral effects of novel stimulation methodologies (de Graaf and Sack 2010). At a time when tDCS is increasingly being used, consideration of these issues seems relevant to investigators in the fields of cognitive, neurophysiology, and systems neuroscience. If we continue to use the unihemispheric montage because of its improved focality, then we will need to increase group sizes or choose more sensitive behavioral probes. In summary, our findings demonstrate that stimulating the left M1 improves motor skill learning relative to sham if hand data are collapsed. Our results give rise to two hypotheses that could be pursued in future studies. They suggest caution against assuming that stimulation of one M1 will have behavioral effects identical to stimulation of the other M1, a consideration especially important for neuro-modulatory studies in patients with unilateral brain damage. Finally, they document stronger effects of bihemispheric than unihemispheric tDCS on motor skill learning, underlining the need for proper power calculations before testing behavioral effects of novel stimulation methodologies.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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