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Modulating activity in the motor cortex affects performance for the two hands differently depending upon which hemisphere is stimulated

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Abstract

We modulated neural excitability in the human motor cortex to investigate behavioral effects for both hands. In a previous study, we showed that decreasing excitability in the dominant motor cortex led to a decline in performance for the contralateral hand and an improvement for the ipsilateral hand; increasing excitability produced the opposite effects. Research suggests that the ipsilateral effects were mediated by interhemispheric inhibition. Physiological evidence points to an asymmetry in interhemispheric inhibition between the primary motor cortices, with stronger inhibitory projections coming from the dominant motor cortex. In the present study, we examined whether there is a hemispheric asymmetry in the effects on performance when modulating excitability in the motor cortex. Anodal and cathodal transcranial direct current stimulation were applied to the motor cortex of 17 participants, targeting the non-dominant hemisphere on one day and the dominant hemisphere on another day, along with one sham session. Participants performed a finger-sequence coordination task with each hand before and after stimulation. The dependent variable was calculated as the percentage of change in the number of correct keystrokes. We found that the effects of transcranial direct current stimulation depended upon which hemisphere was stimulated; modulating excitability in the dominant motor cortex significantly affected performance for the contralateral and ipsilateral hands, whereas modulating excitability in the non-dominant motor cortex only had a significant impact for the contralateral hand. These results provide evidence for a hemispheric asymmetry in the ipsilateral effects of modulating excitability in the motor cortex and may be important for clinical research on motor recovery.

Introduction

In the human brain, homonymous regions of the primary motor cortices (M1) are connected by transcallosal fibers running through the posterior body and isthmus of the corpus callosum (Wahl *et al.*, 2007). There is evidence that the transcallosal connection between primary motor cortices is mainly inhibitory (Ferbert *et al.*, 1992), such that activity in the M1 of one hemisphere inhibits activity in the other hemisphere. This relationship, known as interhemispheric inhibition (IHI), may enable the movements of one hand by dampening neural activity for the other (Duque *et al.*, 2007). Neurological disorders leading to damage in motor regions in one hemisphere, such as stroke, can involve abnormal disinhibition that impedes recovery (Murase *et al.*, 2004; Takeuchi *et al.*, 2005). By understanding the behavioral effects of IHI in healthy individuals, it may be possible to advance treatments that facilitate motor recovery by restoring a normal balance of inhibitory projections between the brain hemispheres.

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Previous studies support an interhemispheric asymmetry in the effects of modulating excitability in M1. Pal *et al.* (2005) found that decreasing excitability in the dominant (left) M1 with transcranial magnetic stimulation (TMS) led to a decrease in IHI from the left M1 onto the right; additionally, excitability in the right M1 increased, presumably due to a release of that area from IHI (Gilio *et al.*, 2003). However, studies have not found a homologous pattern of results when modulating excitability in the non-dominant M1 (Wassermann *et al.*, 1998; Gorsler *et al.*, 2003). Other research showed that IHI from the dominant M1 is stronger than that from the non-dominant M1 (Netz *et al.*, 1995) and that IHI from the dominant M1 may have a greater impact on motor performance (Kobayashi *et al.*, 2004). Studies addressing the transfer of motor learning between hands (Halsband, 1992; Schulze *et al.*, 2002; Garry *et al.*, 2004) also identify a principal role for the dominant motor cortex.

Transcranial direct current stimulation (tDCS) is a non-invasive technique that increases or decreases the resting membrane potential of neurons (Nitsche & Paulus, 2000). The polarity of stimulation determines the effects; anodal tDCS increases excitability, whereas cathodal tDCS decreases excitability. Activity in sodium and calcium ion channels mediates tDCS effects, as does the efficiency of receptors for *N*-methyl-D-aspartate neurotransmitters (Liebetanz *et al.*, 2002;

Nitsche *et al.*, 2003a). tDCS can influence cognitive and behavioral skills associated with the stimulated brain area (Rogalewski *et al.*, 2004; Iyer *et al.*, 2005).

In our previous study (Vines *et al.*, 2006a), we investigated the effects of applying either cathodal or anodal tDCS to the dominant M1 of participants, using a finger-sequencing task to measure performance of one hand at a time. We found effects on performance for both hands. The ipsilateral effects might have resulted from the influence of IHI on the opposite motor region. The present study sought to determine whether hemispheric dominance influences the effects of modulating cortical excitability. We hypothesized that applying tDCS to the non-dominant M1 would produce the same contralateral effects as the dominant M1, whereas the ipsilateral effects would differ between the two hemispheres.

Materials and methods

Participants

Seventeen healthy adults participated in the experiment after giving their informed, written consent following the protocol approved by the Beth Israel Deaconess Medical Center ethics review board. All participants were right handed, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Participants were not screened for typing or instrument performance skill. Six of the participants had taken part in an earlier study investigating the effects of stimulating just the left motor cortex (Vines *et al.*, 2006a); these participants, referred to hereafter as 'continuing' participants, only underwent right-hemisphere motor-cortex stimulation for the current protocol, whereas the other 11 participants, whom we will refer to as 'new' participants, underwent both right- and left-hemisphere stimulation.

Procedure

Participants underwent 2 days of testing. On each day, there was one session for anodal and one for cathodal tDCS, administered while the participants sat in an office chair. On the first day, participants also underwent one session of sham tDCS. For the anodal and cathodal sessions, 1 mA tDCS was applied for 20 min. On one of the testing days, the active electrode was positioned over the participant's left-hemisphere motor region, centered on C3 of the 10–20 international electroencephalogram system; on the other day, the active electrode was positioned over the motor region of the right hemisphere (centered on C4 of the 10–20 electroencephalogram system). The correspondence between C3, C4 and the primary motor cortices of the left and right hemispheres, respectively, has been confirmed by neuroimaging studies (Homan *et al.*, 1987; Herwig *et al.*, 2003; Okamoto *et al.*, 2004), including our own pilot study using high-resolution (1 mm 3 voxel size) magnetic resonance imaging ($n = 5$). A number of TMS and tDCS studies have used the 10–20 electroencephalogram system to identify the location of brain structures for stimulation (Kincses *et al.*, 2003; Rogalewski *et al.*, 2004; Fregni *et al.*, 2005; Iyer *et al.*, 2005; Vines *et al.*, 2006b). Due to the size of the electrode (16.3 cm^2), the stimulation may have extended into premotor cortex and anterior parietal cortex. Consecutive stimulation sessions were separated by a 'wash-out period' of at least 30 min, with an average of approximately 60 min. This was found to be a sufficient duration in our own previous experiments and according to the literature; although studies have found that physiological effects from tDCS can last for 90 min beyond the period of stimulation (Nitsche & Paulus, 2001; Siebner *et al.*, 2004), there have been no reports of effects on behavior lasting longer than 30 min after a single session of tDCS (Rogalewski *et al.*, 2004; Hummel *et al.*, 2005; Ohn *et al.*, 2007). The primary comparison in the study was between the effects of stimulation sessions for the two hemispheres, which were separated by at least 24 h. The ordering for the targeted hemisphere (right and left), stimulation conditions (anodal, cathodal and sham) and hand that first performed the unimanual task (left and right) were all counterbalanced across participants. The six continuing participants had already undergone the protocol with left motor-cortex stimulation and thus they all had right hemisphere stimulation second; this was taken into account in the overall counterbalancing.

A battery-driven, constant-current stimulator (Phoresor, Iomed Inc., Salt Lake City, UT, USA) delivered the 1 mA electrical current to the participant's scalp by means of a saline-dampened active electrode (area 16.3 cm^2) secured over the target motor region and a reference electrode (area 30 cm^2) positioned over the supraorbital region contralateral to the targeted hemisphere. This location for the reference electrode was functionally ineffective in the experimental design (Nitsche *et al.*, 2003b). For both anodal and cathodal stimulation, the tDCS current ramped up over the first few seconds and then remained on for the remainder of the 20 min stimulation period. The sham control session was identical to the anodal and cathodal sessions, except that the experimenter reduced the current to zero after it ramped up for 30 s; the current then stayed at zero for the remaining time period. Participants reported a tingly or itchy sensation at the start of the stimulation, which typically faded away after a few seconds. This sensation was present for both real and sham tDCS. Gandiga *et al.* (2006) found that naive participants were not able to distinguish between real and sham tDCS, as employed in a manner similar to the present study. Participants read a book or magazine during the stimulation and wash-out periods.

Task

The task instructions for a single trial were to use the numbered keys from '2' to '5' on a standard computer keyboard to repeat a unimanual pattern of five sequential keystrokes as accurately and as many times as possible within 30 s. Subjects were shown which numbers of the numeric keypad corresponded to their fingers (see Fig. 1 for further details). During the task, the number sequence was displayed on a computer screen placed in front of the participant. The task interface did not provide any feedback about errors. Prior to any testing, on both days, there were two warm-up trials for each hand. For testing, participants performed three trials of the unimanual finger-sequence task with their right and left hands before and immediately after each tDCS period. Task performance for all three trials lasted approximately 2 min including short breaks between 30 s periods. Participants were tested with a different keystroke pattern for each stimulation condition. Within any one stimulation condition, the pre- and post-stimulation sequences were always the same. Keystroke patterns of equal difficulty were identified with pilot testing. The ordering of keystroke patterns was counterbalanced across participants and stimulation conditions.

To summarize the experimental procedure, each day of the experiment began with a short warm-up lasting about 3 min. Participants then performed the experimental task lasting about 4 min, stimulation was applied for 20 min and then participants performed the task again for 4 min. A wash-out period ensued if there was another stimulation condition to follow. The first day of the experiment included three stimulation conditions, whereas the second day of the experiment included two stimulation conditions.

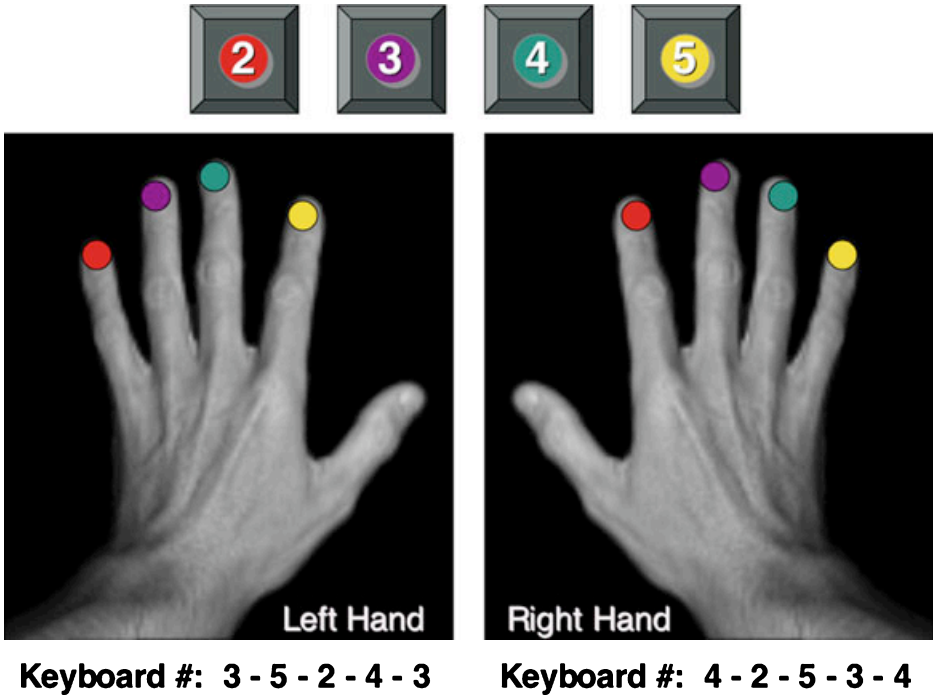

FIG. 1. Unimanual, explicit finger-sequencing task. Example sequences for the right and left hands. The unimanual finger-sequence coordination task involved placing the index, middle, ring and little fingers over the numbers '2'–'5' on a standard keyboard, as shown. Colors in the figure show the correspondence between fingers and number keys. The sequences for the two hands always formed a mirror image such that the same fingers moved in the same order.

Data analyses

We calculated the dependent variable as the percentage of change in the total number of correct sequential keystrokes over three trials, comparing performance before and after tDCS, i.e. the calculation of the dependent variable took the following form: [(post-trial 1 + post-trial 2 + post-trial 3) − (pre-trial 1 + pre-trial 2 + pre-trial 3)]/(pre-trial 1 + pre-trial 2 + pre-trial 3).

This calculation preserved the sign of the performance change, whether positive or negative. A preliminary analysis of the entire dataset showed that there were trials across subjects and conditions that had many errors. In order to avoid skewing the analysis with these outlying data, we developed a very conservative regimen for eliminating outliers. Outliers were identified as 30 s trial periods for which the number of errors was greater than two SDs above the mean number of errors across all 30 s trial periods. If a trial was identified as an outlier, we removed not only that particular trial from further analyses but also the corresponding pre- or post-stimulation trial. For example, if the first 30 s period in a pre-stimulation trial set was an outlier, we also removed the first 30 s period in the corresponding post-stimulation trial set. For all 17 participants, we identified 15 outliers in total, including 10 pre-stimulation outliers, out of a total of 510 trials. The maximum number of outliers within an experimental condition was three, out of 102 trials per condition. The maximum number of outliers for a participant was four across all conditions, out of a total of 30 trials per participant.

As in our previous study (Vines *et al.*, 2006a), we focused on the comparison between up-regulating (anodal tDCS) and down-regulating (cathodal tDCS) excitability. We used the sham tDCS condition as an informative baseline to gauge how much natural improvement might be expected without any real tDCS. To determine whether the left-hemisphere data could be combined for the new and continuing participants, we applied four independent-sample *t*-tests to compare the two groups in each real stimulation condition (anodal and cathodal) for each hand (left and right). No significant differences between the new and continuing participants' data emerged. We combined all of the data and entered them into a three-way repeated measures ANOVA, with factors 'hemisphere' (left and right), 'hand' (left and right) and 'tDCS condition' (cathodal, anodal and sham). Because we only collected sham data on the first day of testing, the same sham data were used for both the left and right hemispheres. Planned *post hoc* analyses with paired-sample *t*-tests compared the effects of cathodal, anodal and sham tDCS for each hand, within each hemisphere; *t*-tests for the primary dependant variable (percentage of change in the number of correct keystrokes) were one-tailed, based upon predictions set by our previous findings (Vines *et al.*, 2006a). We also applied a Bonferroni correction with a factor of two to these tests. Each independent set of data (e.g. data for right-hand performance with anodal stimulation over the right motor cortex) was included in only two *post hoc* comparisons.

Results

All 17 participants completed the experimental procedures. The independent-samples *t*-tests comparing the continuing participants' left-hemisphere data with the new participants' left-hemisphere data yielded no significant differences, with *P*-values ranging between 0.97 and 0.27 [two-tailed, $t(15)$]. These results justified combining all of the data for the remaining analysis.

Data for both the left and right hemispheres, for all participants, are shown in Fig. 2. The average change in performance was positive for all conditions. The three-way repeated measures ANOVA, with factors 'hemisphere', 'hand' and 'tDCS condition', yielded no main effects. There was, however, a significant interaction between the factors 'hemisphere' and 'tDCS condition' ($F_{2,15} = 4.478$, $P = 0.030$) and a

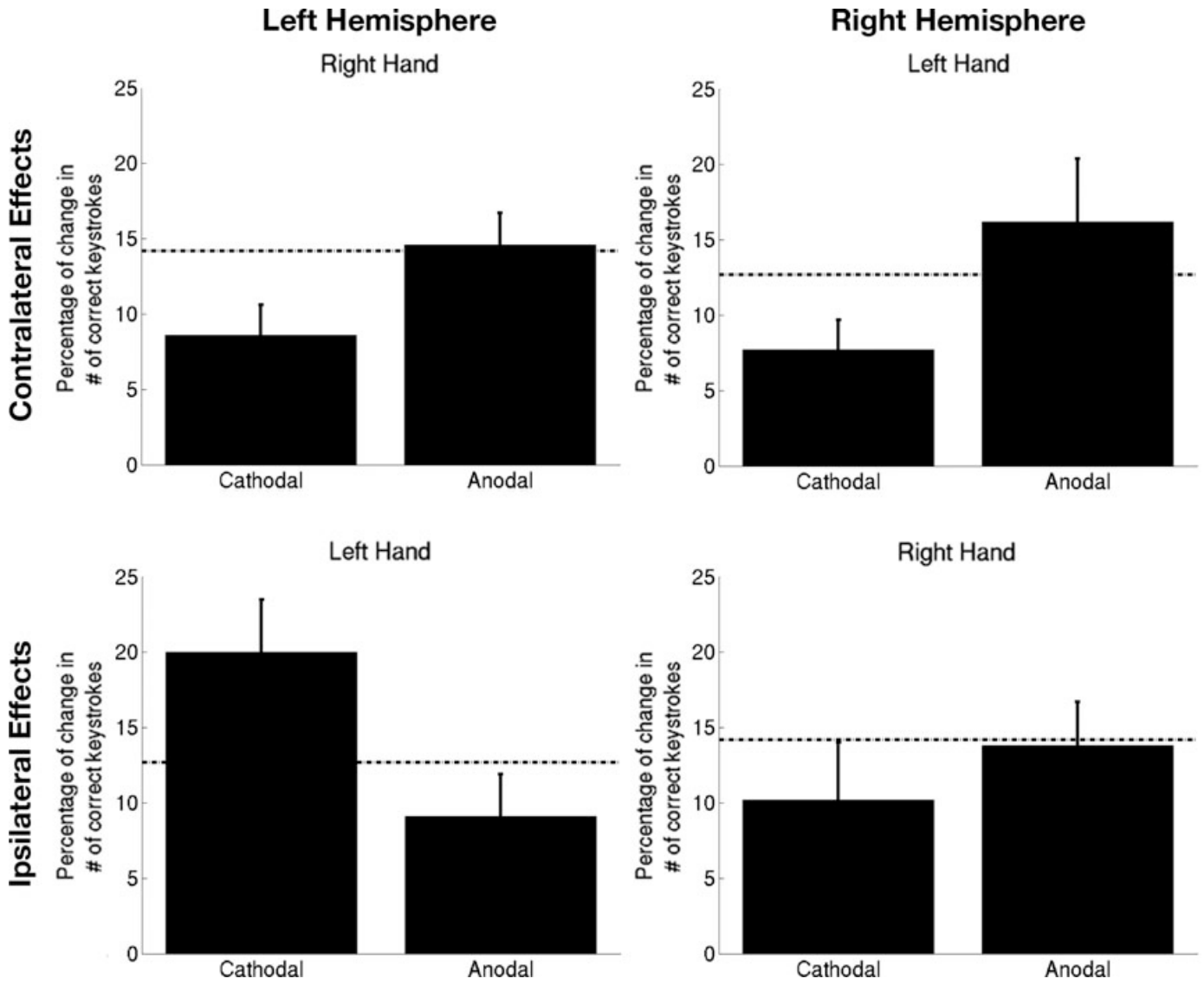

FIG. 2. Mean percentage of change in the total number of correct sequential keystrokes. These results are for all subjects (n = 17). The dotted line represents the mean percentage of change for sham stimulation. Error bars show the SEM. tDCS over the left motor cortex significantly affected the right (cathodal < anodal) and left (anodal < cathodal) hand, whereas tDCS over the right motor area only significantly affected the left hand (cathodal < anodal) with no significant ipsilateral effect for the right hand.

three-way interaction involving the factors 'hemisphere', 'hand' and 'tDCS condition' ($F_{2,15}$ = 9.464, P = 0.002). These results show that the effects of 'hand' and 'tDCS condition' depended upon which hemisphere was stimulated. The *post hoc* analyses revealed significant contralateral (P = 0.011) and ipsilateral (P = 0.002) effects due to applying tDCS over the left motor cortex. In accordance with the results of our previous study (Vines *et al.*, 2006a), cathodal tDCS over the left motor cortex led to a decrement in right-hand performance and to an improvement in left-hand performance compared with anodal tDCS. When stimulating the right motor cortex, the effects of cathodal and anodal tDCS were significantly different only for left-hand performance (P = 0.040); there was no significant ipsilateral effect on right-hand performance (P = 0.349). None of the significant effects were due to differences in the pre-tDCS scores (two-tailed independent-sample t-tests comparing the pre-anodal, cathodal and sham tDCS scores for the left and right hands and for both hemispheres all yielded P > 0.1).

Comparing the effects of real stimulation with sham revealed a significant ipsilateral effect for cathodal stimulation over the left motor cortex (P = 0.018); all other direct comparisons with sham yielded a P-value > 0.09. The one significant result suggests that applying cathodal stimulation to the left motor cortex improved performance for the left hand relative to sham tDCS. It is notable that this analysis with sham involves a comparison between the sham data, which were collected on the first day of testing, with the data for real tDCS, which were collected on both days of testing. Any interpretation of this comparison must be made carefully because various factors, such as cortical excitability and participants' attention, may have differed between the two days of testing. As mentioned above, the primary focus of this study was on the contrast between real anodal and cathodal tDCS; sham data were collected as an informative baseline and are included in the analysis as such.

Further analyses explored which aspects of the finger-sequence task contributed to significant changes in performance. We applied

two-tailed, paired-sample *t*-tests to compare the effects of anodal and cathodal tDCS on the proportion of change in rate of keystrokes and on the absolute change in the number of errors. For the left-hemisphere data, the decrement in right-hand performance for cathodal relative to anodal tDCS was associated with a decreased rate of keystrokes [$t(16) = 2.932$, $P = 0.010$]; the improvement in left-hand performance for cathodal relative to anodal tDCS was associated with an increased rate of keystrokes [$t(16) = 3.047$, $P = 0.008$], as well as a decrease in the number of errors [$t(16) = 2.573$, $P = 0.020$]. For the right-hemisphere data, the improvement in left-hand performance for anodal relative to cathodal tDCS was associated with a trend towards an increased rate of keystrokes [$t(16) = 2.028$, $P = 0.060$].

Discussion

We found evidence for a hemispheric asymmetry in the effects of modulating neural excitability in the motor cortex. Applying tDCS to modulate cortical excitability in the dominant (left) hemisphere had a significant impact on performance in both the contralateral and ipsilateral hands. However, applying tDCS to the non-dominant (right) motor cortex only affected the contralateral hand. These results support our hypothesis that the influence of IHI from the non-dominant motor cortex is weak in comparison to the influence of IHI from the dominant motor cortex.

The intact ipsilateral effects for the left (dominant) motor cortex suggest that stimulating this area did modulate inhibitory projections between the primary motor cortices that are relevant to motor performance. We propose that cathodal tDCS over the left motor cortex induced a decrease in excitability there. The decrease in excitability in the left motor cortex dampened inhibitory projections from the left motor area onto the homologous right motor area, which led to an increase in excitability in the right hemisphere. The increased excitability in the right motor cortex facilitated an improvement in performance for left-hand finger movements. Anodal tDCS over the left hemisphere had the opposite effects. We did not find a homologous pattern of results when applying tDCS to the right (non-dominant) motor area.

Our findings agree with those of Duque *et al.* (2007), which also point to an asymmetry in IHI related to motor performance. They showed that IHI from the non-dominant hemisphere was very weak when the dominant hand performed a motor task, whereas IHI from the dominant hemisphere was strong when the non-dominant hand performed a motor task. Duque *et al.* (2007) posited that this asymmetry facilitates highly accurate control over fine motor movements for the dominant hand by dampening interference from the non-dominant motor cortex.

Although our study revealed that ipsilateral effects on finger-sequence coordination were different for the two hemispheres, effects on the contralateral hand were similar. Whether stimulating the dominant or the non-dominant motor cortex, cathodal tDCS led to a significant decrement in finger-sequence coordination for the contralateral hand relative to anodal tDCS. Evidence supports a relation between heightened motor-cortical excitability and improved performance. Garry *et al.* (2004) showed that practising a motor behavior increases neural excitability in the motor cortex. Enhanced excitability in the contralateral motor cortex has also been observed following extensive practice of simple finger movements (Koeneke *et al.*, 2006) and seems to be an integral physiological attribute of motor learning. Therefore, increasing excitability with tDCS, whether directly or through IHI, may promote learning by inducing a physiological state that is ideal for acquiring a motor skill. Conversely, a tDCS-induced decrease in excitability may impede improvement on a motor sequencing task.

It is notable that left-hemisphere anodal stimulation led to a stronger trend for improved contralateral performance relative to right-hemisphere stimulation. A similar pattern of results arose in a study by Boggio *et al.* (2006), who found improvements in contralateral performance when applying anodal tDCS to the non-dominant motor area but not to the dominant motor area. They posited that there was only a beneficial effect for the non-dominant hand because the dominant hand already performed at a ceiling level prior to stimulation, whereas the less-often-used non-dominant hand could improve further. It is also notable that Jäncke *et al.* (2004) showed that decreasing excitability in the dominant motor cortex with slow repetitive TMS eliminated the performance advantage for the dominant hand on a motor tapping task. In accordance with these previous studies, we found that non-invasive brain stimulation could cause a decrement in performance for the dominant hand but not a strong improvement.

Our results point to the potential for stimulating the motor cortex to significantly influence complex motor performance. Previous research has explored the effects of non-invasive brain stimulation on basic motor behaviors associated with M1, such as speed, accuracy and force of movement (Muellbacher *et al.*, 2000; Jäncke *et al.*, 2004; Levit-Binnun *et al.*, 2007). *Post hoc* analyses in the present study revealed that the significant effects of stimulation were driven primarily by changes in the speed of keystrokes; this suggests that influencing processes that are probably mediated by motor cortex, such as accuracy and speed, can have a significant impact at the level of a complex behavior. These findings concur with previous studies showing that modulating neural excitability in M1 influenced finger-sequencing performance (Nitsche *et al.*, 2003b; Robertson *et al.*, 2005). It is also pertinent that the finger-sequencing task involves a life-relevant behavior, i.e. typing, which would be an ideal target for motor-recovery therapies.

The experimental design used for the present study excludes the possibility of determining at which stage of motor processing tDCS had a significant impact. The 20 min stimulation period may have influenced post-stimulation motor performance, the process of consolidating the motor pattern established during the pre-stimulation task performance or both. Muellbacher *et al.* (2000) found evidence supporting the role of M1 in early motor-memory consolidation. They showed that decreasing excitability in M1, using TMS, specifically disrupted consolidation of motor memory without affecting basal performance levels. The results of Muellbacher *et al.* (2000) would suggest that the effects of tDCS on finger-sequence coordination found in the present study resulted from an impact of tDCS on early consolidation of motor memory. However, it is possible that tDCS influences performance at a different stage of motor processing compared with TMS. Additionally, the ipsilateral effects on task performance may have been driven by a different neural mechanism than the contralateral effects. Further research addressing these issues would be valuable to clinical research on tDCS and motor rehabilitation.

The issue of how IHI affects motor performance is highly relevant to research on motor recovery after stroke (Nair *et al.*, 2007). Damage to one motor area due to a unilateral lesion can disrupt the balance of IHI between the motor cortices. The undamaged motor cortex may become overactive due to a decrease in the inhibitory influence from the damaged hemisphere; a further decrease in the activity of the damaged motor cortex may occur due to an increase in IHI from the undamaged hemisphere (Takeuchi *et al.*, 2005). Such a progressive

imbalance may impede recovery of motor function in the affected hand (Murase *et al.*, 2004) and lead to mirror movements in the unaffected hand (Wittenberg *et al.*, 2000).

Researchers have utilized non-invasive brain stimulation (tDCS or TMS) as a diagnostic tool for monitoring motor recovery after stroke (Koski & Dobkin, 2005) and as an experimental therapy to facilitate recovery. Under the assumption that a unilateral stroke leads to an imbalance in IHI, which in turn might interfere with recovery, two possible modes of experimental intervention have been explored: (i) increasing excitability and up-regulating activity in the affected motor area or (ii) decreasing excitability in the non-affected motor region in order to dampen the transcallosal inhibitory influence of the non-affected motor region onto the affected hemisphere (Fregni *et al.*, 2005; Hummel *et al.*, 2005; Mansur *et al.*, 2005; Takeuchi *et al.*, 2005; Hummel & Cohen, 2006; Talelli & Rothwell, 2006). Our results raise the possibility that applying the first approach (increasing cortical excitability in the damaged hemisphere) would be efficacious for patients with damage to either the dominant or non-dominant motor cortex, whereas applying the second approach (decreasing excitability in the undamaged hemisphere) would be most effective for patients with damage to the non-dominant hemisphere. Fregni *et al.* (2005) noted that decreasing excitability in the undamaged motor area had the strongest effect when the damage was in the non-dominant hemisphere, in accordance with our results and expectations.

The relevance of results from healthy participants to understanding stroke recovery may be limited. It is possible that processes involved in the recovery of motor function after stroke are different from those involved in normal motor performance. Therefore, modulating cortical excitability in the non-dominant motor cortex may have very different effects on ipsilateral motor performance when the balance of IHI has been disrupted by damage due to stroke (Murase *et al.*, 2004; Boggio *et al.*, 2006). The present findings do not preclude the potential for down-regulating activity in the non-dominant, undamaged motor area to benefit performance for the paretic arm. However, by taking asymmetric IHI into account, it may be possible to predict outcomes more accurately and to guide the choice of treatment in future clinical research and therapies for facilitating motor recovery after stroke.

In general, our results point to a complex relationship involving IHI between the motor cortices of the two hemispheres. The findings are highly relevant to the learning and consolidation of motor skills, and to possible hemispheric differences in facilitating or interfering with these effects. Based upon the outcome of this study, we propose that the choice of new experimental treatment strategies that might have an effect on motor recovery after unilateral stroke should take into account whether the dominant or non-dominant hemisphere has been damaged.

Abbreviations

IHI, interhemispheric inhibition; M1, primary motor cortex; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

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