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## Interhemispheric Modulation Induced by Cortical Stimulation and Motor Training

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**Background.** Interhemispheric inhibition might be a beneficial cortico-cortical interaction, but also might be maladaptive in people with neurological disorders. One recently revisited technique that has been shown to be effective in improving motor function in people with stroke using interhemispheric modulation is transcranial direct current stimulation (tDCS).

**Objective.** The aim of this study was to investigate the effects of tDCS combined with unilateral motor training with contralateral hand restraint on interhemispheric inhibition between the dominant and nondominant hemispheres of the brain and on motor performance in participants who were healthy.

**Design.** This was a double-blind, prospective, single-center study with participants who were healthy.

**Methods.** Twenty participants who were healthy were randomly assigned to receive either active or sham tDCS of the primary motor cortex (M1) bilaterally combined with unilateral motor training and contralateral hand restraint. A blinded rater assessed motor function and cortical excitability, including assessment of transcallosal inhibition (TCI).

**Results.** There was a larger increase in motor performance in the nondominant hand for the active tDCS group compared with the sham tDCS group. In addition, a decrease in cortical excitability in the dominant hemisphere and a decrease in TCI from the dominant to nondominant hemisphere were observed for the active tDCS group only. The TCI decrease in the active tDCS group was correlated with motor performance improvement for the nondominant hand.

**Limitations.** Limitations of this study included missing the effect of intracortical inhibition due to a floor effect, not using the optimal tDCS montage, and not being able to assess the effects of other variables such as gender due to the small sample size.

**Conclusions.** The results indicate that tDCS enhances the effects of unilateral motor training and contralateral hand restraint on motor function, and this benefit is associated with a different mechanism of action characterized by bihemispheric modulation in which TCI from the dominant to the nondominant hemisphere is decreased. Transcranial direct current stimulation might be a useful tool to enhance the motor effects of constraint-induced movement therapy.



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The concept of interhemispheric inhibition has been studied for many years, beginning in 1940 with Curtis, who was among the first researchers to stimulate one hemisphere of the brain and measure an evoked response in the opposite hemisphere.<sup>1</sup> Many researchers have observed the behavioral and neurophysiological effects of interhemispheric interactions.<sup>2-4</sup> Although this neurophysiological parameter has been intensively described for the motor system,<sup>5-8</sup> interhemispheric inhibition also is an important physiological mechanism of interhemispheric interactions for attention,<sup>2,4,9</sup> memory,<sup>10,11</sup> and mood.<sup>12,13</sup>

Interhemispheric inhibition might be beneficial, such as during the execution of unimanual movements<sup>14</sup> in people who are healthy, or it might be maladaptive in people with certain neurological diseases such as stroke. In people with stroke, for instance, there is an increase in the excitability of the unaffected hemisphere, presumably due to reduced transcallosal inhibition (TCI) from the damaged hemisphere and increased use of the intact hemisphere.<sup>15</sup> Although this mechanism might be beneficial during acute phases of stroke, once the injury is stable, excitatory input to the perilesional area would seem to be best to maximize the capability of the preserved neurons in the injured tissue to drive behavioral output. For this reason, increased TCI from the unaffected hemisphere seems undesirable in people with stroke. Indeed, modulation of interhemispheric interactions with transcranial magnetic stimulation (TMS) to decrease TCI has been used successfully to promote speech and motor recovery in people with stroke.<sup>16,17</sup>

One recently revisited technique that has been shown to be effective in improving motor function in peo-

ple with stroke using interhemispheric modulation is transcranial direct current stimulation (tDCS).<sup>18,19</sup> Transcranial direct current stimulation has some advantages over other techniques of noninvasive brain stimulation. First, the small size of the electrodes and stimulator allow for greater portability during motor training. Second, tDCS is potentially able to stimulate both hemispheres simultaneously, thereby increasing activity in one hemisphere and decreasing it in the opposite hemisphere, as shown by a recent modeling study.<sup>20</sup> This technique, however, has not been tested in humans. Last, the effects of tDCS are long lasting; 13 minutes of stimulation can change brain excitability for up to 90 minutes.<sup>21</sup>

One important aspect of tDCS is that this technique is truly neuromodulatory, as it changes the membrane resting potential, thereby rendering the stimulated cortical area ready to be modulated by external stimuli, via behavioral intervention.<sup>18,19,22,23</sup> Therefore, we aimed to explore whether the effects of a behavioral intervention (ie, constraint-induced movement therapy [CIMT]) that is associated with the idea of decreasing activity of one hemisphere to release activity of the opposite hemisphere can be enhanced by active tDCS of the motor cortices. Our hypothesis was that active tDCS combined with unilateral motor training with contralateral hand restraint induces a larger motor function improvement and differential changes in cortical excitability compared with sham tDCS with the same motor training therapy.

We decided to study people who were healthy because the performance differences between the non-dominant and dominant hands can be used to explore interhemispheric differences and their consequences on motor function. In a previous

study, Boggio et al<sup>24</sup> demonstrated that anodal tDCS applied to the primary motor cortex of the nondominant hand resulted in increased motor function, as measured by the Jebsen-Taylor Hand Function Test (JTHF). Finally, although previous studies have shown changes in cortical activity with the application of CIMT<sup>25,26</sup> and tDCS,<sup>24</sup> to our knowledge, no one has explored the neurophysiological correlation using a combination of motor training and tDCS, particularly its effects on interhemispheric inhibition. Therefore, we explored this concept in people who were healthy, assessing: (1) whether unilateral motor training with contralateral hand restraint changes TCI and (2) whether tDCS can modulate activity and, when combined with unilateral motor training with contralateral hand restraint, enhance the behavioral effects due to paradoxical facilitation. Because of the differential activity between the nondominant and dominant motor cortices, we elected to perform this study using participants who were healthy as an initial step. Participants poststroke have a shifted balance of interhemispheric inhibition that depends on lesion du-

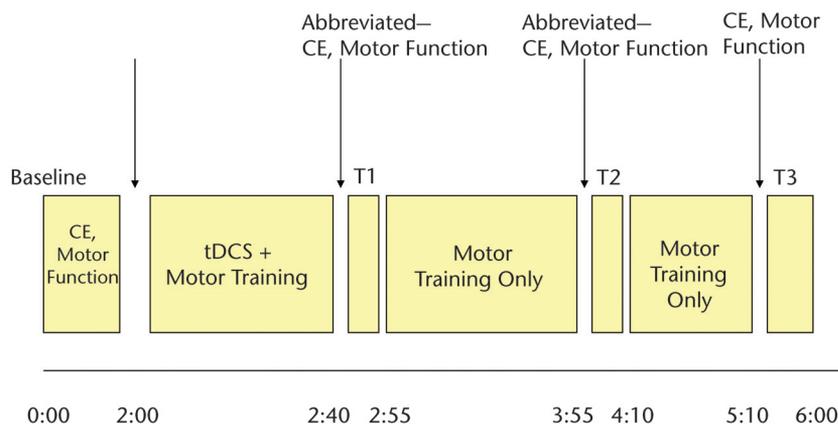


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- **eTable 1:** Shaping Tasks Used in the Study During Motor Training
- **eTable 2:** Intracortical Inhibition and Facilitation
- **eTable 3:** Interhemispheric Inhibition
- **eTable 4:** Correlation Values for the Active Transcranial Direct Current Stimulation (tDCS) Group
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## Interhemispheric Modulation Induced by Cortical Stimulation and Motor Training



**Figure 1.**

Diagram of study flow, showing time in hours. CE=cortical excitability, motor function=assessment of motor function with behavioral testing, motor training=unilateral motor training using contralateral hand restraint, tDCS=transcranial direct current stimulation, T1=measurement taken of nondominant hand after tDCS treatment ended, T2=measurement taken of nondominant hand 2 hours into motor training, and T3=measurements taken of both dominant and nondominant hands after completion of motor training.

ration and location, thus adding a significant source of variability. Therefore, studying people who are healthy is important to understand the core features of interhemispheric interactions and ultimately guide therapeutic interventions in patients poststroke.

## Method

### Participants

Twenty right-handed participants (14 female, 6 male) who were healthy were tested. Their mean age was 20.4 years (SD=1.7, range=19–24). All participants were right handed, as assessed by the Edinburgh Handedness Inventory (participants had to score above 80% on this scale [range=80%–100%]); therefore, we refer to them here as right-handed, left-hemisphere-dominant participants. All participants were college students and thus shared the same level of education. The study was performed in accordance with the Declaration of Helsinki (1964) at the Berenson-Allen Center for Noninvasive Brain Stimulation, Boston, Massachusetts. Written informed consent was obtained

from all participants before inclusion in the study, which was approved by the Human Subjects Review Committee of Harvard Medical School.

### Study Design

A diagram of the study flow is presented in Figure 1. Baseline measurements for each participant were obtained for the following measures: (1) motor function, as indexed by the JTHF; (2) cortical excitability, as measured by motor-evoked potentials (MEPs) from the left and right hemispheres; (3) intracortical inhibition (ICI) and intracortical facilitation (ICF), using the paired-pulse technique; and (4) TCI, using an ISI of 10 milliseconds. All of the cortical excitability measurements were based on the motor threshold for the first dorsal interosseous muscle in both the right and left hands.

After baseline measurements were obtained, the participants were randomly assigned to receive either active tDCS and unilateral motor training with contralateral hand restraint (active tDCS group) or sham tDCS and unilateral motor training with

contralateral hand restraint (sham tDCS group) using the strategy of block randomization and with equal distribution (1:1). One important aspect here is that this trial was truly double blind, as neither the coinvestigator performing the treatment and evaluations nor the participant was aware of which treatment was being used. It was possible to blind the investigator administering the treatment, as we used a device that allows the use of a code to determine whether the treatment was active or sham. Only one investigator, who was not involved with treatment or evaluation, knew the code. After baseline measurements were obtained, unilateral motor training with contralateral hand restraint was performed for 3 hours with 2 breaks in order to perform intermittent evaluations. During the first 40 minutes of motor training, tDCS was applied.

All participant evaluations (JTHF, cortical excitability, TCI) were performed at 4 intervals throughout the study. First, initial (baseline) measurements were taken prior to the start of tDCS and unilateral motor training with contralateral hand restraint. After the tDCS treatment ended, a second measurement was taken of only the nondominant hand (time point 1 [T1]). Two hours into the unilateral motor training, a third measurement was taken using only the nondominant hand (time point 2 [T2]). Finally, after the unilateral motor training was completed, the last evaluations were done, taking measurements from both the dominant and nondominant hands (time point 3 [T3]). Assessments were not made with the dominant hand at T1 and T2 due to the need for restricting the dominant hand during unilateral motor training.

Participants were trained on the JTHF (they performed 10 training trials in order to reach a stable plateau). Procedures for this test were fol-

lowed according to the original description by Jebsen et al.<sup>27</sup> Participants performed practice trials, baseline trials, 2 abbreviated trials (which recorded only the nondominant hand during unilateral motor training with contralateral hand restraint), and a final evaluation for each hand.

### Study Intervention Procedures

**Transcranial direct current stimulation.** Direct current stimulation was applied using a pair of saline-soaked sponge electrodes (size 35 cm<sup>2</sup>) and delivered by a specially developed, battery-driven, constant current stimulator\* with a maximum output of 10 mA. The anode electrode was placed over the right (nondominant) primary motor cortex (M1), and the cathode electrode was placed over the left (dominant) primary motor cortex (M1). We used the 10/20 international electroencephalographic system for electrode placement, in which M1 corresponds to C3 or C4. The rationale of this montage is to increase excitability (with anodal tDCS) in the hemisphere of the hand that is being trained (nondominant hand) and decrease it in the hemisphere of the dominant hand (with cathodal tDCS) to decrease TCI. This montage has been shown to be effective, according to our modeling study.<sup>20</sup>

For the active conditions, participants received 1-mA tDCS for 40 minutes (with 10 seconds of ramp-up and ramp-down) concurrent with the beginning of unilateral motor training. The same procedure was used for sham stimulation, but current was applied just for the first 30 seconds. This procedure is reliable to blinded participants for the respective stimulation condition.<sup>28</sup>

One participant complained of nausea at the start of tDCS during the unilateral motor training. At that time, the participant was evaluated by the study physician and was released from further participation. Other mild adverse effects such as mild headache and scalp tingling were observed in a small number of participants but did not interfere with their participation in this study.

### Unilateral motor training with contralateral hand restraint.

At the same time as the tDCS was set up, a hand mitt (Skil-Care Rigid Palm Padded Mitt<sup>†</sup>) was placed on the participants' dominant hand. This mitt remained on throughout the entire 3-hour period when unilateral motor training was being performed with the nondominant hand. Participants were not allowed to remove the mitt, and a piece of tape was placed over the edge to monitor whether they attempted to remove it. Participants were supervised by study staff who helped to direct them throughout the entire period the hand mitt was worn. Nine different shaping tasks were used during this 3-hour period, which included buttoning a shirt, pouring water, and folding towels (see the complete list in eTab. 1, available at [ptjournal.apta.org](http://ptjournal.apta.org)). All 9 tasks were performed using the left (nondominant) hand only. During the 3-hour period, the participants were able to complete, on average, 3 repetitions of each task (given the time to complete the tasks and the small interval between them), and all participants completed a minimum of 2 sets of all 9 tasks during the 3-hour period the hand mitt was worn.

### Study Assessment Procedures

We used single-pulse TMS to measure corticospinal excitability. Focal TMS was performed using a commer-

cially available figure-of-eight coil (outside diameter of each wing=7 cm) and 2 Magstim 200 stimulators that were coordinated using a Bistim device.<sup>‡</sup> Initially, we ensured that the muscle was completely relaxed by online monitoring with surface electromyographic activity at high gain (10–50  $\mu$ V). Optimal scalp position for induction of MEPs was determined following published guidelines.<sup>29</sup> The coil was held tangentially to the skull with the handle pointing occipitally with an angle of 45 degrees to the midline of the participant's head. To determine the threshold intensity, stimulation was initiated at 65% (or higher, if needed) of the maximum stimulator output and decreased in 5% increments, or 2% of the maximum stimulator output, when near the threshold level. The *motor threshold* was defined as the lowest stimulation intensity to produce at least 5 MEPs with peak-to-peak amplitudes of 50  $\mu$ V from 10 consecutive stimuli. The mean values for motor threshold in the right and left hemispheres, respectively, were 45% and 43% stimulator output intensity. Optimal scalp position and motor threshold were determined at baseline.

We then recorded MEPs by adjusting the TMS intensity to achieve an MEP in the first dorsal interosseous muscle of about 1-mV peak-to-peak amplitude, and intensity was maintained constant throughout the experiment. We recorded 10 MEPs for each time point. The MEP gives a measure of global corticospinal excitability.<sup>30</sup>

To measure ICI and ICF, we used the paired-pulse technique, in which a subthreshold stimulus delivered using TMS can modulate a subsequent test MEP delivered a few millisec-

\* NeuroConn GmbH, Eldith, Ilmenau, Germany.

† AliMed Inc, 297 High St, Dedham, MA 02026.

‡ Magstim Company Ltd, Spring Gardens, Whitland, Carmarthenshire, Wales, United Kingdom SA34 0HR.

onds after the conditioning stimulus.<sup>30</sup> The mechanisms involved with this modulation are based on inter-neuronal activity; therefore, it can measure ICI and ICF, depending on the interval between pulses. Maximum inhibitory effects are found when the ISIs are between 1 and 4 milliseconds; when the interval is longer (ie, 9–15 milliseconds), facilitation can be seen.<sup>30</sup> Therefore, for the paired-pulse measurement, a first (subthreshold) conditioning stimulus (using an intensity of 90% of motor threshold) was applied, followed at a variable ISI by a second (suprathreshold) test stimulus (using an intensity of 130% of motor threshold) applied to the same location at which the first stimulus was applied.<sup>31</sup> We used the following ISIs: 2, 3, 6, 10, and 12 milliseconds. Various ISIs were randomized and inter-mixed with control trials (test stimulus alone). For each ISI, 5 trials were averaged, and the resulting MEP amplitude was converted to a percentage of the control MEP amplitude. Paired-pulse parameters were expressed as the amount of inhibition (for ICI, we used ISIs of 2 and 3 milliseconds) and facilitation (for ICF, we used ISIs of 10 and 12 milliseconds). Paired-pulse measurement was performed only at baseline and at the end of unilateral motor training with contralateral hand restraint (T3).

In order to assess interhemispheric interactions, we used the technique of bi-hemispheric stimulation, which also used a paired-pulse sequence (but in this case, stimulation was delivered to both motor cortices). The notion here is that inhibitory and excitatory interactions are constantly transferred between hemispheres. Therefore, if a suprathreshold stimulus is applied to the motor cortex of one hemisphere (using an intensity of 120% of motor threshold) and 10 milliseconds later a suprathreshold stimulus is applied to the contralat-

eral motor cortex (using an intensity of 130% of motor threshold), this later MEP will be modulated by the first pulse. The period of inhibition is between 10 and 15 milliseconds after the minimum corticospinal conduction time to the recorded hand muscle cortical area.<sup>30</sup> This inhibition is mediated via transcallosal pathways and originates within the motor cortex. We calculated the percentage of inhibition for each stimulus before and after treatment was performed.

Transcranial magnetic stimulation output intensities were maintained from baseline measurements through final evaluations in order to allow for comparison of results from the beginning of the experiment to the final measurements. The electromyographic activity was amplified with a band-pass filter between 10 and 2,000 Hz, and the signal was digitized at a frequency of 5 kHz using a PowerLab 4/25T device<sup>§</sup> and stored on a computer for offline analysis using the Scope software (version 4.0.8).<sup>§</sup>

### Data Analysis

The main outcome measures in this study were: (1) motor function change, as indexed by the JTHF, and (2) TCI, as assessed using TMS. For motor function, the dependent variable was performance on the JTHF, and the independent variables were time of stimulation and treatment group. We, therefore, performed a mixed analysis-of-variance (ANOVA) model, including as covariates the fixed-effect variables of treatment group, time of stimulation, and group×time interaction and the random-effect variable of participant ID. We performed a similar model to assess TCI, but in this analysis we used percentage of MEP inhibition as a dependent variable. When appro-

<sup>§</sup> ADInstruments Inc, 2205 Executive Cir, Colorado Springs, CO 80906.

prate, *post hoc* analyses were conducted using Bonferroni correction for the pair-wise comparisons. We assessed other parameters of cortical excitability (MEP changes and TCI) as an exploratory analysis and, therefore, not correcting for multiple comparisons. Finally, we performed pair-wise correlations between changes in parameters of cortical excitability and motor function changes, as indexed by the JTHF, as an exploratory analysis (without correction for multiple comparisons) using the Pearson correlation test.

## Results

### Motor Function Assessment

We initially compared baseline motor function, as indexed by the JTHF, between the active and sham tDCS groups and found no significant differences ( $P>.05$ ). However, there was a differential improvement in motor function, as indexed by JTHF, between the active and sham tDCS groups (Fig. 2). The group × time interaction was significant ( $F_{3,54}=3.02, P=.037$ ) for the left (nondominant) hand. The overall results showed that there was a larger improvement in the active tDCS group compared with the sham tDCS group: mean (SD) motor function change between baseline and T3 was  $8.9\% \pm 7.8\%$  in the active tDCS group and  $3.9\% \pm 4.9\%$  in the sham tDCS group ( $t_{18}=1.7, P=.05$ ). Both groups had a differential improvement across time points. For the active tDCS group, there was a tendency for a differential effect between baseline and T1 (immediately after tDCS) ( $t_9=1.7, P=.06$ ) and a significant effect between T2 and T3 ( $t_9=3.7; P=.008$ , corrected  $P$  value), but there was no significant difference between T1 and T2 ( $t_9=0.49, P=.3$ ). For the sham tDCS group, the only significant difference was between T1 and T2 ( $t_9=4.1; P=.004$ , corrected  $P$  value); there was no difference between baseline and T1 ( $t_9=1.2, P=.14$ ) or between T2 and

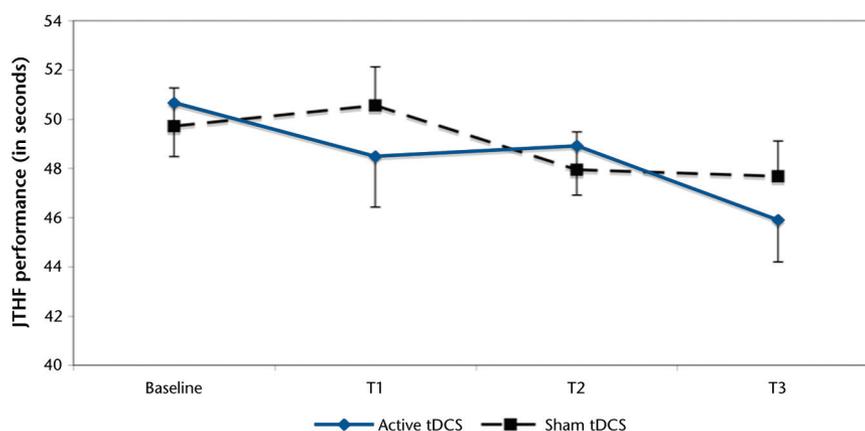
T3 ( $t_9=0.85$ ,  $P=.8$ ) (Fig. 2). We performed a similar analysis for the right (dominant) hand. The group  $\times$  time interaction was not significant ( $F_{1,18}=0.1$ ,  $P=.75$ ), suggesting that tDCS was not associated with motor function changes in the dominant hand.

### Cortical Excitability Assessments Motor-evoked potential analysis.

We initially measured MEPs before and after training and stimulation in both hemispheres (Fig. 3). We performed 2 ANOVA models, as the time point assessments were different for the left and right hemispheres. The analysis for the left and right hemispheres is shown below.

A mixed ANOVA model showed a significant group  $\times$  time interaction ( $F_{1,18}=12.59$ ,  $P=.0023$ ) for the left (dominant) hemisphere (corresponding to the restricted right hand), suggesting a differential change in cortical excitability when comparing active and sham tDCS. *Post hoc* analysis revealed that active tDCS was associated with a significant mean (SD) reduction in MEP amplitude of  $19.8\% \pm 21.4\%$  in the dominant hemisphere ( $t_9=3.9$ ;  $P=.004$ , corrected  $P$  value), but there was no significant change in the sham tDCS group (mean [SD] increase of  $0.8\% \pm 8.3\%$ ,  $t_9=0.45$ ,  $P=.65$ ) (Fig. 2).

For the right (nondominant) hemisphere (corresponding to the nondominant trained hand), we initially performed an ANOVA with all data points and found only a tendency for a significant interaction ( $F_{3,54}=2.00$ ,  $P=.1$ ) and a tendency for a significant time effect ( $F_{3,54}=2.61$ ,  $P=.06$ ). Because these results suggested that there was a change in cortical excitability in the same direction in both groups, we performed an exploratory analysis (as this was decided *post hoc*) considering only 2 time points (baseline and T1). This analy-



**Figure 2.**

Changes in Jebsen-Taylor Hand Function Test (JTHF) scores from the beginning to the end of the experiment. A decrease in the amount of time necessary to complete the test was observed in both the active transcranial direct current stimulation (tDCS) group and the sham tDCS group. The active tDCS group improved performance by the first evaluation after baseline and had greater improvement compared with the sham tDCS group. Error bars represent the standard error or the mean. T1=measurement taken of nondominant hand after tDCS treatment ended, T2=measurement taken of nondominant hand 2 hours into motor training, and T3=measurements taken of both dominant and nondominant hands after completion of motor training.

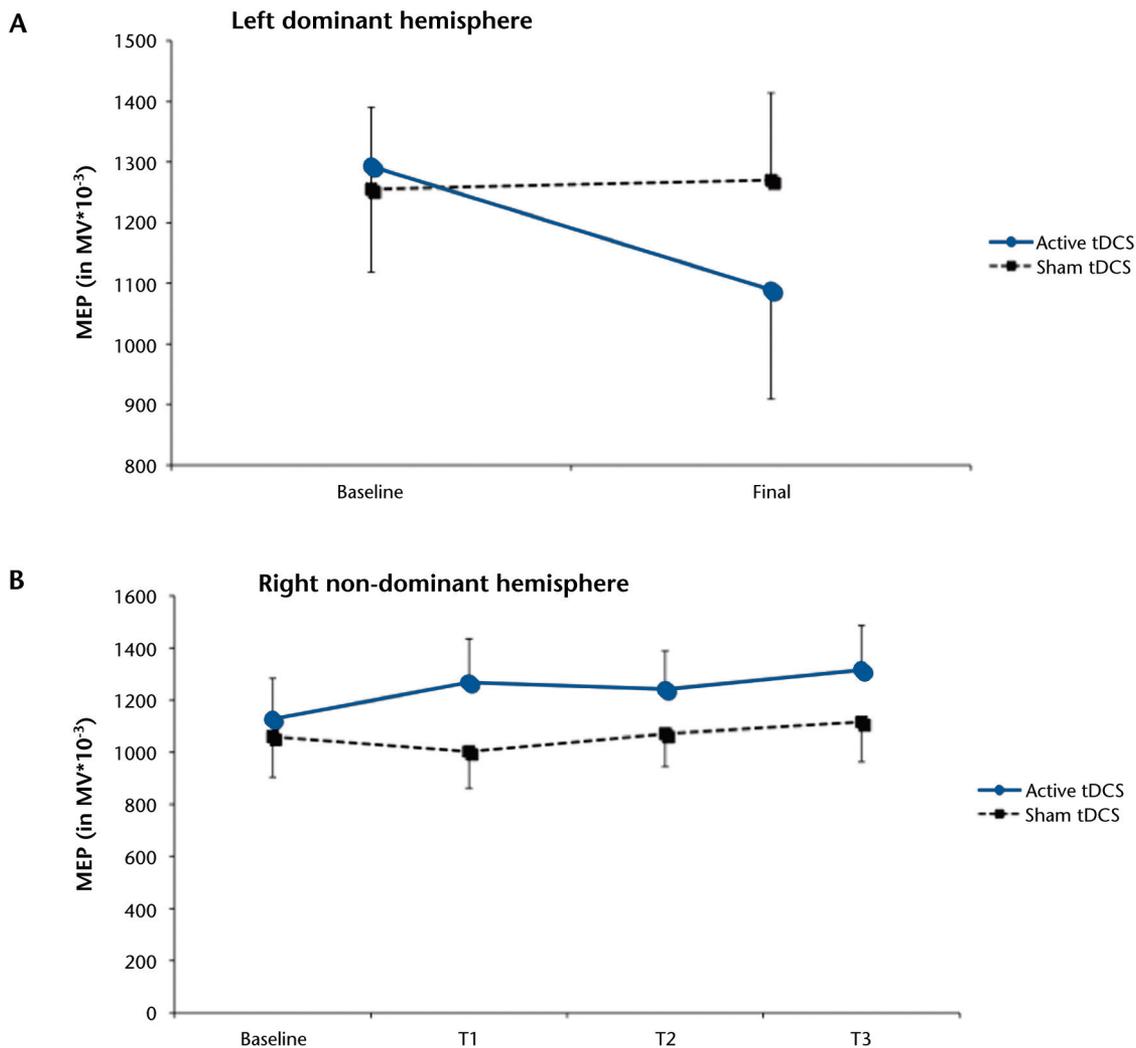
sis showed a significant group  $\times$  time interaction ( $F_{1,18}=6.50$ ,  $P=.02$ ). There was a significant increase in MEP amplitude after active tDCS (mean [SD] increase of  $13.8\% \pm 14.2\%$ ,  $P=.013$ ) and no significant change after sham tDCS (mean [SD] decrease of  $5.6\% \pm 23.4\%$ ,  $P=.46$ ). Interestingly, the active tDCS group had a rapid increase of MEP amplitude after stimulation and then had only a small increase, and the sham tDCS group had a delayed increase in MEP amplitude. At the end of the study, although there was a larger increase in MEP amplitude from the nondominant hemisphere in the active tDCS group compared with the sham tDCS group ( $20.1\% \pm 25.8\%$  versus  $10.0\% \pm 19.2\%$ ), this difference was not significant (between-group comparison,  $t_9=.98$ ,  $P=.17$ ) (Fig. 3).

**Intracortical inhibition and facilitation analysis.** The analysis of intracortical excitability changes for the left and right hemispheres did not show any significant changes for either the left (dominant) hemi-

sphere or the right (nondominant) hemisphere. For ICI analysis, the group  $\times$  time interaction was not significant for the left hemisphere ( $F_{1,18}=0.06$ ,  $P=.8$ ) or for the right hemisphere ( $F_{1,18}=0.16$ ,  $P=.69$ ). Similar results were obtained for the ICF analysis: no significant group  $\times$  time interaction was found for the left hemisphere ( $F_{1,18}=0.06$ ,  $P=.8$ ) or the right hemisphere ( $F_{1,18}=0.11$ ,  $P=.74$ ). In addition, the term effect was not significant in all of these models, suggesting that ICI and ICF did not change over time regardless of treatment ( $F<1$  for all models) (eTab. 2, available at [ptjournal.apta.org](http://ptjournal.apta.org)).

### Transcallosal inhibition analysis.

For TCI, we initially analyzed inhibition from the left (dominant) hemisphere to the right (nondominant) hemisphere (Fig. 4). The mixed ANOVA showed a significant group  $\times$  time interaction for left to right inhibition ( $F_{1,18}=6.89$ ,  $P=.017$ ), and the *post hoc* results showed that TCI significantly decreased by  $44.2\% \pm$



**Figure 3.**

Motor-evoked potential (MEP) changes for the active transcranial direct current stimulation (tDCS) group and the sham tDCS group: (A) Change in MEP amplitude from the beginning to the end of the experiment in the dominant hemisphere. The sham tDCS group showed no change in MEP amplitude, whereas the active tDCS group showed a significant decrease in MEP amplitude in the dominant hemisphere. (B) Change in MEP from the beginning to the end of the experiment in the motor cortex (M1) of the nondominant hemisphere. Both groups showed an increase in MEP amplitude; however, the active tDCS group showed a significant increase by the first evaluation and had a greater overall increase compared with the sham tDCS group. Error bars represent the standard error of the mean. Note that the dominant hand (corresponding to the dominant hemisphere of the brain) had the mitt on for the duration of the experiment; therefore, MEP could be assessed only 2 times for the dominant hemisphere. T1=measurement taken of nondominant hand after tDCS treatment ended, T2=measurement taken of nondominant hand 2 hours into motor training, and T3=measurements taken of both dominant and nondominant hands after completion of motor training.

30.5% after active tDCS ( $t_9=3.1$ ;  $P=.012$ , corrected  $P$  value). Although TCI (left to right) increased after sham tDCS treatment by  $16.5\pm 46.3\%$ , this change was not statistically significant ( $t_9=1.4$ ,  $P=.18$ ). For TCI from the right hemisphere to the left hemisphere, the mixed ANOVA showed that the

group  $\times$  time interaction was not significant for either the sham tDCS group or the active tDCS group ( $F_{1,18}=3.42$ ,  $P=.08$ ) (Fig. 4). Finally, because the participants' sex might have an effect on TCI, we added this variable in the model, and the results showed that this variable was not significant for either model (left to

right and right to left TCI,  $P>.05$  for both models) (eTab. 3, available at [ptjournal.apta.org](http://ptjournal.apta.org)).

**Correlations**

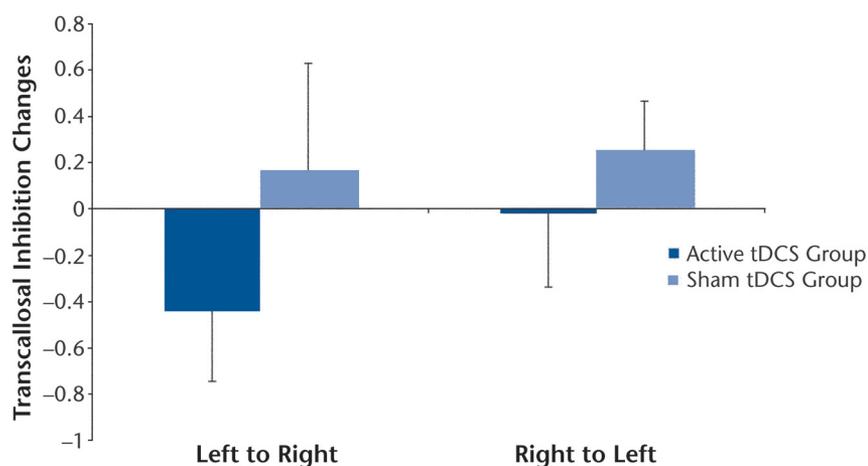
We performed correlations between motor function changes (as indexed by the JTHF) and changes in cortical excitability (changes in TCI from left

to right hemisphere and from right to left hemisphere and changes in MEP in the left and right hands) for the active and sham tDCS groups (eTab. 4 [available at [ptjournal.apta.org](http://ptjournal.apta.org)] and Fig. 5). For the active tDCS group, there was a significant correlation between changes in motor function (baseline versus T2) and changes in TCI from left to right hemisphere ( $r = -.72$ ,  $P = .018$ ), indicating that the changes in motor function in the nondominant hand were associated with a decrease in TCI (Fig. 5) from the dominant hemisphere to the nondominant hemisphere. A significant correlation also was found between changes in MEP in the left hand and motor function improvement in this hand ( $r = .72$ ,  $P = .018$ ). For the sham tDCS group, there was no significant correlation between any of these variables (eTab. 4, available at [ptjournal.apta.org](http://ptjournal.apta.org)).

Finally, in order to test whether TCI changes, regardless of the treatment, are associated with motor function changes, we performed similar correlations including both groups together. This analysis showed no significant correlation ( $r = .2$ ,  $P = .39$ ).

## Discussion

Our results show that both the sham and active tDCS groups had significant improvements in motor function in the nondominant hand as indexed by the JTHF after 1 day of testing, during which there was 3 hours of motor training. The active tDCS group showed a greater improvement after the first evaluation, whereas the sham tDCS group showed gradual improvement over the course of the experiment. The MEPs recorded from the nondominant hand in both groups also increased similarly in amplitude over the course of this experiment; however, in the active tDCS group, there was a significant decrease in MEP

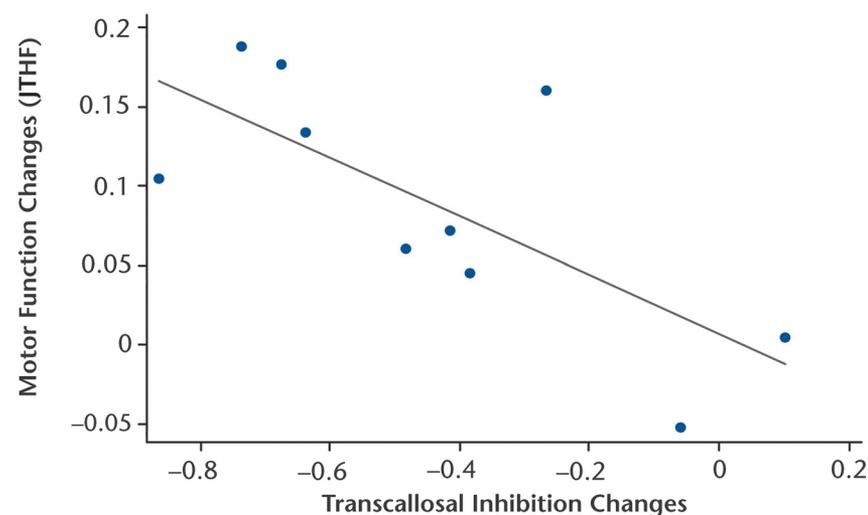


**Figure 4.**

Changes in transcallosal inhibition from left to right hemisphere and from right to left hemisphere measured as a percentage of baseline for the active transcranial direct current stimulation (tDCS) group and the sham tDCS group. The only significant change was a decrease in transcallosal inhibition from the left to right hemisphere after active tDCS. Error bars represent the standard error of the mean.

amplitude in the dominant hand. In summary, for both JTHF and MEP assessments, the tDCS active group showed a statistically significant enhancement after the first evaluation,

and the sham tDCS group showed gradual increases over the course of the experiment for the nondominant hand. Transcallosal inhibition from right to left hemisphere in the active



**Figure 5.**

Correlation of the change in Jebsen-Taylor Hand Function Test (JTHF) scores and change in transcallosal inhibition (TCI) from left (dominant) to right (nondominant) hemisphere for the active transcranial direct current stimulation (tDCS) group. As the time necessary to complete the JTHF decreased, the TCI from the left to right hemisphere also decreased.

and sham tDCS groups and from left to right hemisphere in the sham tDCS group did not result in any statistically significant changes. The active tDCS group, however, showed a statistically significant decrease in TCI from left to right hemisphere. This decrease in TCI, along with the increased amplitude of the MEP in the nondominant hemisphere of the active tDCS group, correlated with increased performance of the JTHF in the nondominant hand.

We discuss these findings with the emphasis on the following points: (1) the effects of unilateral motor training with contralateral hand restraint on motor function in participants who were healthy; (2) enhancement of unilateral motor training effects with tDCS; (3) differential mechanisms of action of unilateral motor training with contralateral hand restraint and unilateral motor training with contralateral hand restraint and tDCS, based on the neurophysiological findings of this study; and (4) use of these findings for future research aiming at clinical gains.

Our trial testing whether tDCS enhances unilateral motor training with contralateral hand restraint is based on the idea of applying these results in participants poststroke receiving CIMT; therefore, we will discuss the use of tDCS as a potential tool to enhance CIMT in people poststroke. Constraint-induced movement therapy was first studied by Taub et al in primates.<sup>32</sup> They observed that after unilateral deafferentation by dorsal rhizotomy, these primates never recovered spontaneous use of the affected upper extremity. Research following this observation showed that the deafferented arm could gain reuse through restriction of the unaffected arm or by retraining the affected extremity.<sup>33</sup> The first research using this technique in humans was

performed in 1993 by Taub et al.<sup>34</sup> In that experiment, the participants had their unaffected hand restricted using a mitt for 90% of their waking hours. These participants also received training of the affected limb for 6 hours a day over a period of 2 weeks.<sup>34</sup> Since this first trial, many other studies have investigated the efficacy of CIMT for improving motor function in the affected limb. In our study, we used the same concept in participants who were healthy. Although participants who are healthy do not have lesions in the corticospinal tract, the increased use of the dominant hand is associated with less dexterity in the nondominant hand and less activity in the nondominant motor cortex<sup>35</sup>; thus, it might be considered a limited functional lesion. In addition, we conducted only 3 hours of unilateral motor training with contralateral hand restraint (which can be viewed as modified CIMT), as we were interested in acute effects only.

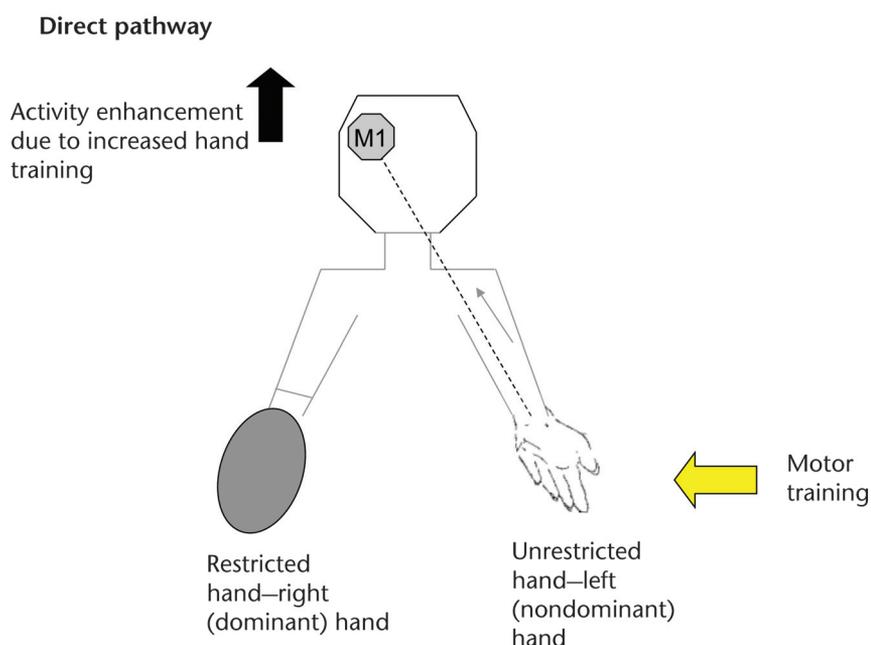
The improvement of motor function in both groups that received our unilateral motor training procedure suggested that it was an effective intervention to enhance motor performance in the nondominant hand in participants who were healthy. A meta-analysis<sup>36</sup> reported that 14 randomized clinical trials have been performed looking at the use of CIMT to improve upper-extremity function. This meta-analysis concluded that CIMT may improve upper-extremity function better than alternative treatments. In addition, previous research indicates that an increase in motor function is correlated with an increase in cortical excitability in the affected hemisphere.<sup>37,38</sup> Similar results were shown in our study, as we observed an increase in MEP amplitude in the nondominant hemisphere in both groups, including the group that received unilateral motor training with contralateral hand re-

straint and sham tDCS; that was correlated with improvement in motor function in the active tDCS group. Therefore, the effects of unilateral motor training with contralateral hand restraint in improving motor function seems to be correlated with an increase in the local motor cortex activity, as indexed by an increase in MEP amplitudes.

One important finding of our study is that we showed that active tDCS enhances the effects of motor training with contralateral hand restraint on motor function. Participants who received active tDCS had a larger and faster improvement in motor function. Transcranial direct current stimulation is a noninvasive type of brain stimulation that uses a small current to modify neural thresholds in brain regions located directly underneath the electrodes. The anode is associated with an increase in cortical activity, and the cathode is associated with a decrease in cortical activity. In this study, the anode was placed over M1 of the nondominant hemisphere, and the cathode was placed over M1 of the dominant hemisphere; thus, our goal was to increase activity in the nondominant hemisphere and decrease it in the dominant hemisphere. This might be viewed as a form of “central CIMT”—that is, of forcing an increase in excitability in the less used hemisphere (in the case of this study, in the nondominant hemisphere) using tDCS as opposed to the traditional method of CIMT, which induces changes in cortical excitability via peripheral modulation. We have shown previously that this strategy improved motor function in the nondominant hand in participants who were healthy<sup>24</sup>; however, in that study, no neurophysiological parameter was measured.

Furthermore, tDCS seems to be a helpful tool to enhance behavioral changes induced by behavioral training such as motor training. The learning of new skills is linked to changes in neuronal activity and cortical excitability.<sup>39</sup> As observed in previous experiments, tDCS is a powerful technique to modulate cortical excitability. Nitsche and Paulus<sup>21,40</sup> showed that anodal tDCS applied to the motor cortex in humans produces a prolonged increase in cortical excitability, most likely through subthreshold neuronal membrane depolarization<sup>41</sup>; thus, it can enhance cortical effects induced by behavioral training, resulting in enhancement of behavioral function. Another advantage is that tDCS modifies spontaneous neuronal activity and, therefore, can increase cortical activity in a more physiological manner, thus priming a given area for a subsequent behavioral intervention such as motor training. Several studies have demonstrated such an effect, for instance, that tDCS improved motor learning in participants who were healthy<sup>24</sup> and in participants poststroke.<sup>18,19</sup> All of these characteristics support the premise that tDCS may be an attractive tool to enhance motor training.

Another important finding of our study is that improvement with unilateral motor training with contralateral hand restraint and sham tDCS is different from that of the same motor training with active tDCS, suggesting different mechanisms of action for both interventions in modulating motor function. When active tDCS is combined with our motor training strategy, improved motor function may be the result of decreased TCI from dominant (left) to nondominant (right) hemispheres, further increasing activity in the nondominant hemisphere, as we showed that TCI was reduced only in the active tDCS group and correlated with motor function changes. A reduction of TCI

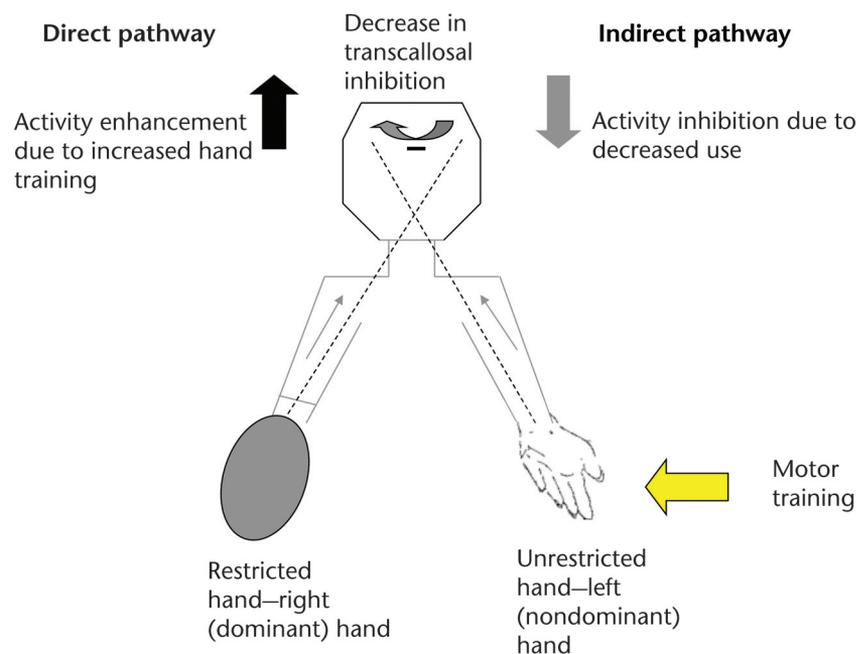


**Figure 6.** Potential mechanism by which constraint-induced movement therapy affects motor function. The results showed that the direct pathway mechanism of action for training of the nondominant hand might be the only mechanism of motor function improvement.

has been shown previously in participants poststroke after inhibitory, low-frequency, repetitive TMS of the unaffected motor cortex.<sup>42</sup> To our knowledge, however, this is the first report of tDCS reducing TCI during training with our modified CIMT procedure (unilateral motor training with contralateral hand restraint) and being associated with motor function changes. In the participants who received sham tDCS, there was no change in TCI; the only change was an increase in amplitude of MEP. This finding suggests that the main mechanism of action of our modified CIMT procedure in participants who were healthy was through direct modulation of the trained hemisphere (affected hemisphere in the case of stroke) and not to the reduction of TCI due to the restriction of the contralateral hand. The only benefit of CIMT, in this context, therefore, seems to be correlated to a forced use of the unrestricted hand.

In summary, there are 2 possible mechanisms through which motor function might be improved: (1) a direct effect (direct pathway) (ie, an increase in cortical excitability in the nondominant hemisphere through increased use of the nondominant hand that results in improved motor function) (Fig. 6) and (2) an indirect effect (ie, an increase in the excitability of the nondominant hemisphere through a decrease in TCI from the dominant hemisphere to the nondominant hemisphere) (Fig. 7). Our study showed that our modified CIMT procedure with sham tDCS was associated only with the first mechanism and, in contrast, that our modified CIMT procedure with active tDCS was associated with both direct and indirect mechanisms (Figs. 6 and 7).

This experiment is an important step in the planning of new treatments for survivors of stroke. A meta-



**Figure 7.**

With active transcranial direct current stimulation (tDCS), another mechanism of action takes place: the indirect pathway (ie, decreased use of the dominant hand due to the mitt decreases cortical activity, thus decreasing transcallosal inhibition from dominant to nondominant hemisphere and contributing to the increase in local activity and motor function in the nondominant hand).

analysis assessing studies that used CIMT treatment after stroke concluded that CIMT may provide better treatment as opposed to standard therapies.<sup>36</sup> However, the beneficial effects of CIMT are still limited. Transcranial direct current stimulation combined with CIMT may increase improvement in motor function through the combination of: (1) a direct effect on motor cortex excitability in the affected hemisphere induced by both tDCS and CIMT and (2) decreased TCI from the unaffected hemisphere to the affected hemisphere through the use of tDCS. The combination of these 2 techniques also may decrease the amount of time necessary to complete treatment, making it more feasible for patients and therapists. Previous studies and analysis have shown that both therapists and patients had con-

cerns about the length of time for treatment in CIMT.<sup>36,43,44</sup>

This research has demonstrated differences in the mechanism of action by which unilateral motor training with contralateral hand restraint alone and this same procedure combined with tDCS affect motor improvement in the nondominant hand of participants who are healthy. The increased improvement that was observed during the first evaluation, and throughout the remaining time points of this study, suggests that tDCS combined with CIMT might be a beneficial strategy, and we, therefore, encourage further studies in patients poststroke.

**Limitations**

The effects of ICI may have been missed due to a floor effect. To ad-

dress this issue, additional testing would be necessary to calculate the optimal conditioning stimulus for ICI. Increasing testing time would greatly extend the duration and potentially overburden participants. The length of time to complete the experiments was already substantial: approximately 7 to 8 hours per participant. Additionally, there were no tendencies for changes in ICI.

Another potential limitation is the montage we chose, in which both motor cortices are stimulated simultaneously. This montage was not shown to be effective in the study by Nitsche and Paulus.<sup>40</sup> However, we have shown in our modeling study<sup>20</sup> that this montage induces a significant current in the motor cortex, and the current study demonstrates that active tDCS compared with sham tDCS results in significant changes in motor function and corticospinal excitability. The potential discrepancy here might be due to the duration of stimulation. In the study conducted by Nitsche and Paulus,<sup>40</sup> the authors used 1 mA for up to 10 minutes. In our study, we used 1 mA for 40 minutes. Given that duration of stimulation is critical to induce changes in cortical excitability, this difference in duration of stimulation might explain the difference in the results of these 2 studies.

Finally, although we found no effects of the participants' sex for the TCI analysis, this result might have been due to the lack of power of this analysis because of the small sample size and asymmetric sex distribution. A previous TMS study showed that women have a higher TCI compared with men, suggesting that interhemispheric connectivity in the anterior half of the trunk of the corpus callosum might be different between men and women.<sup>45</sup>

Dr Pascual-Leone and Dr Fregni provided concept/idea/research design, fund procurement, and facilities/equipment. All authors provided writing and project management. Ms Williams provided data collection and clerical support. Ms Williams and Dr Fregni provided data analysis. Dr Pascual-Leone provided institutional liaisons.

The study was approved by the Human Subjects Review Committee of Harvard Medical School and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

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## **Interhemispheric Modulation Induced by Cortical Stimulation and Motor Training**

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