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Focal and bi-directional modulation of lower limb motor cortex using anodal transcranial direct current stimulation

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Abstract

Background—Because we are interested in non-invasive transcranial brain stimulation as an adjuvant to post-stroke walking therapy, we applied direct current stimulation (tDCS) preferentially to either the left or right lower limb motor cortex (M1) in two separate sessions and assessed the resulting modulation in both cortices.

Objective/Hypothesis—We hypothesized that tDCS applied preferentially to one lower limb M1 of healthy subjects would induce between-hemisphere opposite sign modulation.

Methods—Transcranial magnetic stimulation (TMS) with the coil offset 2 cm either side of vertex was used to assess the percent change in rectified motor evoked potential (MEP) area recorded bilaterally from vastus lateralis (VL) and tibialis anterior (TA) of 10 subjects during weak tonic contraction.

Results—ANOVA revealed an up-regulation of the target cortex and a down-regulation of the non-target cortex ($p = 0.001$) and no effects of hemisphere (left, right) or muscle (TA, VL). Significant modulation was evident in 78% of VL and TA muscles (all $p < 0.05$). Excitability *increased* in 60%, but *decreased* in 18%. For 43% when excitability increased, a simultaneous decrease in excitability was evident in homologous muscle responses providing support for our hypothesis.

Conclusions—The results indicate a modest effectiveness and focality of anodal tDCS when applied to lower limb M1, suggesting in a human model that the strength and depth of polarizing cortical currents induced by tDCS likely depend on inter-individual differences in the electrical properties of superficial brain structures.

Keywords

Transcranial magnetic stimulation; Transcranial direct current stimulation; Lower limb; Cortical excitability

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INTRODUCTION

Transcranial direct current stimulation (tDCS) has been used in psychiatric and motor system research for many years (1–4). This non-invasive technique has not only been used to probe motor system excitability, but recently it has also been applied as an upper limb motor system therapy (5,6). However, few studies have reported the effects of tDCS applied over the lower limb primary motor cortex M1. A recent study demonstrated that facilitatory anodal tDCS applied near the vertex induced an increase in motor excitability assessed using transcranial magnetic stimulation (TMS), with the tibialis anterior both at rest and during voluntary contraction (7). Modulation during tonic muscle contraction, was robust (~ 40% of baseline excitability) and persistent, lasting for at least an hour. Interestingly, cathodal tDCS which suppresses the excitability of hand muscle cortical representations, failed to induce an effect in this study, a finding consistent with our own unpublished observations. In a recent study we applied anodal tDCS to the lower limb representations of chronic subcortical stroke patients (8). Typically tDCS is applied using a 35 cm² saline soaked anode. In an attempt to enhance focality we used an oblong 8 cm² anode placed over the ipsilesional hemisphere so that one edge was aligned with the mid-sagittal plane and the mid-point of the electrode was aligned with the coronal plane. We expected that this orientation would preferentially stimulate the ipsilesional M1. Although there was considerable between-subject variability of motor excitability assessed during walking, there was an effect of hemisphere where ipsilesional excitability increased and contralesional excitability decreased (8). The study suggested that tDCS modulates target lower limb motor cortex with a reasonable measure of focality. Notwithstanding these results, motor cortices in both hemispheres are likely to modulate with the same sign because of the close proximity to each other either side of the central fissure.

The literature generally acknowledges that low spatial focality is a limitation of tDCS (9). Modeling indicates that the majority of the applied current is shunted through the scalp (10), and a small proportion of the current will follow the cerebrospinal pathways and architecture of the brain's superficial layers before reaching deeper cortical layers. To the best of our knowledge only one study has formally examined the focality of tDCS (9). This study was conducted on hand muscle cortical representations. The authors set out to shape the effects of tDCS by manipulating electrode size and current density. They found that tDCS, with a 3.5 cm² anode placed over the abductor digiti minimi representation, failed to modulate the excitability of the neighboring representation of the first dorsal interosseus (FDI) muscle. The “hot-spot” for the FDI representation (determined with TMS) lay just outside of the physical boundary of the anode. Our own lower limb data following ipsilesional tDCS which achieved opposite sign modulation in each hemisphere (11) together with the results from Nitsche et al. (2007) suggest at least a modest measure of focality is attainable providing electrode placement, electrode size, and current density are carefully chosen.

The present study was motivated by our long term interest in the development of non-invasive brain stimulation as an adjuvant to walking therapy following stroke. Stroke typically results in an asymmetry of between-hemisphere motor excitability (12), and reducing this asymmetry using a repetitive bimanual movement protocol has been associated with improved upper limb function (13). Other studies have reported improved upper limb behavior in stroke patients following suppressive contralesional brain stimulation supporting the notion that re-balancing interhemispheric interactions following stroke may be therapeutic (5,14). Therefore there may also be therapeutic value in the selective up-regulation of one lower limb M1. However, for the lower limb, the close proximity of the two cortices either side of the central fissure is likely a major limitation to achieving the desired direction of modulation in one hemisphere only. The primary aim of the present study was to determine whether the focality previously inferred from *reducing* the asymmetry of between-hemisphere excitability of stroke patients (8) could be demonstrated by *inducing* an asymmetry of between-hemisphere excitability in healthy

subjects. We hypothesized that anodal tDCS applied preferentially to one lower limb M1 of healthy subjects would induce between-hemisphere opposite sign modulation.

A secondary aim was to investigate the presence of ipsilateral cortical connections with lower limb motoneurons. This aim was motivated by cerebral blood flow studies that have demonstrated ipsilateral cortical activation during paretic lower limb muscle contraction in stroke patients (15) and healthy subjects (16). We therefore hypothesized that when a robust between-hemisphere opposite sign modulation was induced, responses to TMS with the coil preferentially located over the up-regulated hemisphere will be larger in the ipsilateral limb following tDCS. Our reasoning for the second hypothesis assumed that responses with the coil placed in the offset ipsilateral position would likely result from a mix of inputs from both cortices due to the magnetic field activating both cortices, or from cortical current spread. Therefore, with the coil offset over the up-regulated cortex, the *balance* of descending inputs to motoneurons would favor those from the ipsilateral cortex, and response amplitude would increase following tDCS. Conversely, with the coil offset over the down-regulated cortex, response amplitude would decrease following tDCS.

MATERIALS AND METHODS

Subjects

Ten healthy subjects (3 females, 7 males; mean age 23 years) with no known neurological disorders were recruited to participate in this study. A brief description of the study was provided and written informed consent approved by the Northwestern University Institutional Review Board was obtained from each subject. All methods conformed to the Declaration of Helsinki. Before inclusion in the study, subjects were screened for contraindications to TMS (the presence of metal implants, cardiac pacemakers, unexplained headaches, history of seizures or medications likely to alter cortical excitability). Each subject attended two sessions of testing separated by a period of several days, although a second data collection session was conducted just over 24 hours after the first session for two subjects. Anodal tDCS was applied preferentially to one lower limb M1 in the first session and to the other M1 in the second session. The order of application to the right and left hemispheres was randomized.

Experimental Protocol

Subjects were seated comfortably in a chair with knees and ankles flexed to 90 degrees and the feet constrained by flexible 4.0 kg weights placed over the dorsum of each foot. EMG was collected bilaterally from the vastus lateralis (VL) and tibialis anterior (TA) muscles. An estimate of maximum voluntary isometric contraction (MVIC) was obtained for each muscle with the subject sitting. During TMS measurements the subject was given real time feedback of EMG on an oscilloscope to match a target contraction corresponding to 10% MVIC for each muscle. TMS was used to generate MEPs from two coil positions – contralateral and ipsilateral – to each muscle being tested (details below). Following the initial TMS measurements, anodal tDCS was preferentially applied to one lower limb M1 followed by post-tDCS TMS measurements. Subjects returned for a second session when anodal tDCS was preferentially applied to the other lower limb M1 and the same TMS protocol was repeated.

Electromyography

Surface Ag/AgCl electrodes (ConMed SureTrace, Utica NY) were placed over the muscle bellies of the VL and TA of both legs. Before affixing the electrodes, hair was removed and the skin cleaned with alcohol to ensure adequate contact. The reference electrode was placed over the right patella. All EMG data were sampled at 2,000 Hz, amplified (1000 ×) and bandpass-filtered (10–500 Hz) using an AMT-8 amplifier (Bortec Biomedical, Canada,

Calgary, AB). EMG data were recorded using Spike2 software (Cambridge Electronic Design, UK).

Transcranial Direct Current Stimulation

tDCS was delivered using a constant current stimulator (Dupel Iontophoresis System, Empi, MN) via an 8 cm² oblong saline soaked sponge anode placed over the leg area of M1 and a self-adhesive carbonized reference cathode (48 cm²) placed on the forehead above the contralateral orbit (Dupel BLUE, MN). Prior to placement of the electrodes, the skin was prepared by cleaning with alcohol. The vertex (taken as the intersection of the inter-aural and nasion-inion lines) was marked on the scalp. The anode was placed lateral to the vertex with the medial edge of the electrode on the mid sagittal line (Figure 1). The electrode midpoint was located on the inter-aural line. In a previous study, Jeffery and colleagues applied 2 mA for 10 minutes with a 35 cm² electrode yielding a current density of 60 $\mu\text{A}/\text{cm}^2$, and a total charge of 34 $\mu\text{C}/\text{cm}^2$ (7). To achieve a current density and total charge similar to this, we chose a stimulation intensity of 0.5 mA for our 8 cm² electrode giving a current density of 60 $\mu\text{A}/\text{cm}^2$ and applied the current for 10 minutes yielding a total charge of 36 $\mu\text{C}/\text{cm}^2$. These density and charge values compare well with those reported in two safety studies which did not reveal adverse effects. In a study where a total charge of ~ 0.6 times the charge applied in the present study was delivered to the motor cortex, Nitsche and colleagues reported no change in the level of serum enolase, a sensitive marker of neural damage with a total charge of 24 $\mu\text{C}/\text{cm}^2$ (4). In a cognition study, Iyer and colleagues applied a total charge of 96 $\mu\text{C}/\text{cm}^2$ to the prefrontal cortex which was ~ 2.6 times larger than the charge we applied in the present study. They reported improved verbal fluency and only transient redness of the scalp in two of their bald subjects (17). In the present study the current was ramped up to 0.5 mA over a 10 s period and a similar but descending current ramp was used at the end of the trial. POST measures began five minutes after tDCS. Apart from mild tingling sensations, no scalp redness or other adverse effects were reported.

Transcranial Magnetic Stimulation

Single pulse TMS was delivered using a Magstim 200 stimulator (Magstim, Dyfed, Wales, UK) via a double cone coil (diameter 110 mm). Spike2 software was used to trigger the stimulator at 0.25 Hz (or less depending on stimulus intensity) and also to record the trigger pulses. A linen cap was tied tightly on the subject's head (over the tDCS electrode). The vertex was marked on the cap. Two positions, 1 cm posterior and 2 cm left of the vertex and 1 cm posterior and 2 cm right of the vertex were marked on the cap. In previous experiments we have found that locating the double cone coil 1 cm posterior to the coronal plane reliably evokes responses in the leg muscles of the majority of subjects. The double cone coil was placed on the cap at either of these 2 cm offset positions where the intersection of the two embedded coils would be over the marked positions. The coil was oriented to induce a posterior–anterior current flow in cortex. The coil cable was supported by a coil holder stand and the coil position was maintained manually by an assistant. The position of the coil was checked constantly during data collection to ensure that the coil was in the same position throughout. The coil placed in the offset left position was used to generate contralateral responses from the right leg and ipsilateral responses from the left leg. The coil placed in the right offset position generated contralateral responses from the left leg and ipsilateral responses from the right leg. Even though we acknowledge all responses are likely a mix of descending volleys from both hemispheres, the term “contralateral responses” refers to motor evoked responses obtained from the leg muscle contralateral to the position of the coil and “ipsilateral responses” refers to motor evoked responses obtained from the leg muscle ipsilateral to the coil position.

Preliminary data revealed that background EMG amplitude during 10% MVIC tonic contraction was typically ~ 0.4 mV peak to peak. Therefore, with the coil over one of the offset

positions, active motor threshold (AMT) was taken as the stimulus intensity resulting in identifiable MEPs of at least 0.4 mV peak to peak in 50% of successive trials from the contralateral VL and TA during individual muscle contractions. We used TMS intensities of 110% AMT to obtain MEPs in the contralateral limb. This intensity was large enough to produce MEPs of sufficient amplitude that would enable increases and decreases in POST amplitude to be revealed. In order to consistently obtain MEPs in the ipsilateral limb of ~ 0.4 mV that could also reveal increases and decreases in POST amplitude, we increased the TMS intensity to 120% AMT. The same procedure was repeated with the coil offset to the other side. Fifteen MEPs were obtained for each muscle at each coil position with only one muscle active at a time, i.e., four sets from each coil position.

Data analyses

Purpose written MATLAB code (The Mathworks, Inc, Natick, MA, USA) was used to analyze all data imported from Spike2. MEP area analysis was chosen as the key primary measure to capture changes in corticomotor excitability induced by the tDCS. During tonic contraction a small increase in motoneuron activity driven by weak descending TMS-induced volleys is difficult to detect as a time invariant peak event. Therefore, the modulation of tonic motoneuron activity resulting from additional motoneuronal firing in response to weak TMS-induced volleys is better captured by calculating the rectified integrated area of EMG within a time window. The “MEP window” was established for each muscle for each subject by finding the onset and offset latencies of large contralateral MEPs in response to strong TMS stimuli. Because the onset latencies of upper limb ipsilateral MEPs are typically several milliseconds longer than contralateral MEPs (18), we extended the window by 10 ms to capture increased motoneuron activity that may have resulted from late arriving descending ipsilateral volleys. A window of identical width was also set prior to the stimulus artifact to measure background EMG activity. EMG area (mV.s) values for background and MEP window were averaged for each muscle, subject, and coil position. Typically a small number of trials (2 or 3 of 15) were deleted to bring background POST and PRE values within 2%. This ensured that PRE and POST mean MEP areas used in subsequent calculations were accompanied by equivalent levels of motoneuron activity. We have found group analysis of MEP amplitude data to be problematic in lower limb EMG collected during muscle contraction mainly due to large inter-subject variability in background EMG amplitude. In the present study MEP amplitudes before and following tDCS were examined with an ANOVA, and POST MEP amplitudes were also normalized to PRE MEP amplitudes for each muscle and subject and were examined with a separate ANOVA.

The change in the size of responses with the coil in the ipsilateral position following tDCS was expected to be consistent with the excitability of the ipsilateral cortex, not the slightly more remote contralateral cortex. This expectation was based on the premise that our TMS technique likely induced responses that were a *combination* of ipsilateral and contralateral descending volleys.

Statistical Analyses

A four way ANOVA with the factors: hemisphere (left vs. right), cortex (target vs. non-target), muscle (VL vs. TA) and time (PRE vs. POST), with time as the repeated factor, was conducted on mean MEP amplitudes. Further, a three way ANOVA with the factors: hemisphere, cortex, and muscle was conducted on POST MEP amplitudes expressed as a percentage of PRE MEP amplitudes. To test for an effect of tDCS in individual muscles, t-tests were conducted to identify muscles from which PRE to POST MEP amplitude differed when the coil was placed in the contralateral position. To test for an effect of tDCS on POST responses normalized to PRE recorded with the coil in the ipsilateral position, t-tests were conducted separately on TA and VL means to determine if they differed from zero, i.e., that significant modulation was

evident. All results were considered significant at an alpha level of 0.05. Statistical analyses were performed using STATA software (StataCorp LP, College Station TX, USA).

RESULTS

Across VL muscles mean AMT was 42 % MSO (range, 34 – 52 %) and across TA muscles, mean AMT was 36 % (range, 40 – 60 %). MEP window widths (including the added 10 ms) ranged from 15 – 68 ms (onset to offset) for the VL and 23 – 60 ms for the TA.

Average PRE and POST rectified MEP areas in mV.s (± 1 SEM) recorded from the contralateral VL with the coil preferentially positioned over the target hemisphere were 7.46 (± 1.7) and 10.14 (± 1.2) respectively, and for the TA 7.19 (± 1.3) and 7.98 (± 1.2) respectively. The ANOVA on PRE and POST MEP amplitudes did not reveal any significant main effects or interactions.

POST MEP area expressed as a percentage of PRE MEP area examined in the three way ANOVA revealed a significant main effect of targeted cortex ($F_{2,9} = 11.83$, $p = 0.001$) where group mean modulation ($\pm$ SEM) for target cortex responses was 26.64 % (± 4.0) and – 8.5 % (± 3.9) from the non-target cortex (Figure 3). No other main effects or interactions (all $p > 0.23$) were detected. Because there were no effects of hemisphere and muscle in the ANOVA, data were pooled resulting in 40 muscle pairs i.e., 10 subjects $\times$ 2 sessions $\times$ 2 muscle pairs (either VL or TA) for subsequent descriptive analyses. Modulation of MEP area was accepted when t-tests indicated mean POST MEP areas differed from zero in both muscles of a pair (responses from target and non-target cortex). Responses in 9 of 40 (22.5%) failed to reach significance therefore modulation was evident in 31 of 40 muscle pairs (all $p < 0.05$). The largest POST mean as a percentage of PRE that did not reach significance was –11 % ($p = 0.14$) and the smallest that reached significance was –5.5 % ($p = 0.05$), both from VL muscles. An inspection of data revealed that the main effect of target hemisphere was driven by responses in some muscles only (Figure 4A). Although the ANOVA revealed positive sign modulation in target cortex, 7 of 40 pairs (18%) modulated with a negative sign (target mean $-27.8\% \pm 5.9$; non-target mean $-7.0\% \pm 9.8$) (Figure 4B). Further, in a different 7 of 40 muscle pairs, facilitation was evident in responses from both target (mean $27.8\% \pm 5.9$) and non-target (mean $7.0\% \pm 9.8$) cortices (Figure 4C). Seventeen of 40 pairs (43%) demonstrated up-regulation (mean, $42.6\% \pm 6.8$) in the target cortex and down-regulation in the non-target cortex (mean, $-25.7\% \pm 4.3$) (Figure 4D).

With the coil preferentially placed over the ipsilateral target cortex t-tests of normalized MEP amplitude revealed significant modulation for TA ($n = 20$, mean 19.5 ± 8.2 , $p = 0.013$), and for VL ($n = 20$, mean 26.7 ± 9.28 , $p = 0.004$). To determine if ipsilateral response size was consistent with the excitability of the ipsilateral cortex, data were examined from the 17 muscle pairs where an increase in target cortex excitability and a decrease in non-target cortex excitability was evident. MEP means from 15 of 17 ipsilateral muscles revealed modulation consistent with the excitability of the ipsilateral hemisphere and responses from the remaining two muscles revealed modulation consistent with the slightly more remote contralateral hemisphere. Representative examples from each of these sub-groups described above are illustrated in Figure 5.

DISCUSSION

In this study we investigated the focality of anodal tDCS applied over the lower limb M1 of healthy individuals. We chose to stimulate the lower limb motor cortex because of our interest in developing adjuvants to lower limb therapy. We used a small electrode, placed to one side of the mid-sagittal line, and delivered a total charge of $36 \mu\text{C}/\text{cm}^2$ which is consistent with the

charge delivered by Jeffrey and colleagues (7). We expected these parameters would enhance focality by virtue of electrode size, placement, and current density.

Analysis of non-normalized MEP amplitude data failed to reveal any significant effects because of between-subject variability in MEP amplitude typically observed in lower limb EMG during muscle contraction. This variability is likely caused by between-subject differences in motoneuron activity and the gain of each corticomotor system. For these reasons analysis of normalized MEP amplitudes (POST as % PRE) is typically conducted during tonic, dynamic, or locomotor-induced contraction of lower limb muscles (7,11,19,20). Normalized data supported our hypothesis that anodal tDCS applied preferentially to one lower limb M1 of healthy subjects induces between-hemisphere opposite sign modulation, despite the close proximity of the two M1s located either side of the central fissure. Individual subject's data showed substantial variations in the after effects induced by anodal tDCS for lower limb muscles suggesting tDCS as applied in the present experiment had modest focality. Surprisingly, *down*-regulation was evident in 18% of tested muscles indicating considerable variability in the polarizing effects of the currents as applied in this study. Data also revealed that when tDCS induced between-hemisphere opposite sign modulation, responses to TMS with the coil preferentially placed over the up-regulated hemisphere were larger in the ipsilateral limb following tDCS.

For responses in nine of the 40 muscle pairs examined, no change was evident in MEP amplitude following tDCS, suggesting polarizing currents were not strong enough to depolarize cortical layers in which the effects of tDCS are revealed with TMS. For seven muscle pairs when MEP amplitudes increased in one muscle, MEP amplitude recorded from homologous muscles also increased indicating that neurons in both target and non-target cortices received similar depolarizing currents. For 17 of 40 muscle pairs when MEP amplitudes increased in one muscle, MEP amplitude recorded from homologous muscles decreased. Responses in this latter group were primarily responsible for the highly significant effect of target cortex revealed by the ANOVA using normalized data. When tDCS induced between-hemisphere opposite sign modulation, and responses to TMS were larger in the ipsilateral limb following tDCS, ipsilateral connections between M1 and the lower limb spinal motoneurons were the likely pathways responsible. To our knowledge, this is the first study to examine the focality of anodal tDCS over the lower limb M1 and to provide evidence of ipsilateral connectivity using TMS.

Several upper limb studies using paired associative stimulation and repetitive TMS have reported substantial inter-individual variability in the after effects of stimulation, the incidence of modulation in the desired direction being ~75% (21–23). In the present study, the incidence (of target M1 facilitation) was lower (60%). What accounts for the inter-individual variability in the sign and extent of modulation observed in the present study? Differences in structure and electrical conductivity of the scalp, skull, and meninges, and the orientation of neurons within cortical layers are likely to result in different current paths and a different susceptibility to depolarizing currents. It is possible that diverse current paths may have also activated non-primary motor areas, although the small anode likely restricted depolarizing currents to the primary motor cortex and supplementary motor area. The relative extent of depolarization and hyperpolarization of neural elements in multiple cortical layers are likely contributors. For the cortical representations of the nine muscles that failed to reveal significant modulation, the most likely explanation is that polarizing currents did not reach appropriate neurons. In these individuals higher currents may have induced the expected modulation. A converse explanation is likely for the cortical representations of the seven muscles that were up-regulated but the opposite cortex was also up-regulated. Clearly there was sufficient current to depolarize target hemisphere cortical neurons, but brain surface and cortical architecture likely allowed current to flow through tissues to the other side of the central fissure. In these individuals a different electrode position or lower currents may have resulted in a more focal modulation. However,

this particular result may have been the result of inaccuracies in anode placement (bridging the central fissure) thereby depolarizing neurons in both hemispheres. In future experiments we will address this issue by using image guided stereotactic placement of electrodes to enhance the accuracy of electrode placement. A number of mechanisms may be responsible for the robust down-regulation of seven cortical representations. One possibility is that hyperpolarization of neurons synapsing with pyramidal tract neurons in deeper layers gave rise to a down-regulation of motor system excitability. This explanation would be consistent with animal research that has demonstrated anodal current hyperpolarizes superficially located cortical neurons resulting in a depolarization of neurons deeper in the cortex, including pyramidal tract neurons (24,25). However, these studies used pulses, not steady-state currents. Other possibilities include the spatial arrangement of neurons (especially those lying in the medial bank of the mid-sagittal fissure), activation of inhibitory interneurons, and homeostatic responses. These results help illustrate that little is known about current pathways and the relationship between polarization of human cortex and strength of current applied through the scalp and skull. However, further studies similar to the present study may help build a better understanding. Regardless of the veracity of these explanations, when designing an experiment using anodal tDCS over the lower limb M1 to modify behavior, the probable relationship between focality, induced current strength, and the spatial arrangement of neurons in the motor cortex should be taken into account. Further, data should be interpreted with caution, and TMS measures should be included to establish that the desired sign and extent of modulation had been achieved.

Another interesting finding from the present study was that when between-hemisphere opposite sign modulation was evident, ipsilateral connectivity could be inferred from MEPs recorded from 15 of 17 muscle pairs. It is highly likely the ipsilateral motor responses resulted from volleys arising in both the down-regulated contralateral non-target and up-regulated ipsilateral target hemispheres. Post-tDCS facilitation of both the contralateral and ipsilateral motor responses, when the TMS coil was placed 2 cm lateral to the mid-sagittal line favoring the facilitated cortex, provided evidence that responses with the coil in the ipsilateral position were *not only* due to volleys descending via contralateral pathways. If our “ipsilateral responses” had been the result of contralateral volleys only, post-tDCS modulation evident in ipsilateral responses would have been consistent with the excitability of the down-regulated hemisphere. In order for there to be facilitation of the ipsilateral responses as demonstrated, the mix of volleys arriving at the spinal motoneurons would have favored those descending from the ipsilateral hemisphere.

Although our study provided some electrophysiological evidence for ipsilateral corticospinal connectivity with lower extremity motoneurons, there are some important caveats that should be considered when interpreting our results. First, the protocol holds well only when an asymmetry of between-hemisphere motor excitability is created. Testing for lower limb ipsilateral connections without this asymmetry makes interpretation of findings difficult because the size of the magnetic field induced by TMS prevents ipsilateral and contralateral contributions from being identified. A modified protocol could be designed to assess ipsilateral connectivity in stroke survivors who already have an asymmetry of between-hemisphere motor excitability. Second, this technique was applied during tonic muscle contractions and these findings should not be construed as evidence that ipsilateral connectivity plays a relevant role during walking. Third, the ipsilateral responses to which we refer are not “ipsilateral motor evoked potentials” (iMEPs) reported in upper limb and axial muscles. The latter are unlikely to result from a mix of contralateral and ipsilateral volleys, whereas our ipsilateral responses almost certainly do. Finally, our results do not address the precise route by which volleys arising from the ipsilateral M1 reach spinal motoneurons.

This study was the first step in our quest to understand the focality of tDCS over the lower limb M1 and examine the presence of physiological ipsilateral connectivity to the lower limb motor neurons in healthy adults. However, much work is yet to be done to build confidence in regard to the choice of electrode size, placement, and current density in order to target cortical regions and obtain the desired sign of induced modulation. A better understanding of the neurophysiological mechanisms of the non-lesioned hemisphere associated with movement has become essential because of the emergence of tDCS in research settings where cortical excitability of the lesioned motor system is purposefully manipulated after stroke. This knowledge may then guide the development of effective therapeutic interventions by rendering the cortex more susceptible to motor therapy, and lead to the individualization of rehabilitation strategies.

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Figure 1.

Schematic representation of tDCS electrode positions and expected outcome. The anode (dark grey) was placed lateral to the vertex with the medial edge of the electrode on the mid sagittal line. The cathode (light grey) was placed over the orbit of the contralateral eye. EMG traces represent pre-tDCS (dotted) and post-tDCS (solid) motor evoked responses (MEPs) obtained from the contralateral hemisphere. Anodal tDCS was expected to cause facilitation of contralateral MEPs evoked from the target cortex and inhibition of MEPs from the non-target cortex.

Figure 2. Representative examples of contralateral motor evoked responses from: A. vastus lateralis (VL) and B. tibialis anterior (TA) muscles showing background and MEP area windows used for analysis. Traces are rectified EMG of a single trial from a single subject. In this example, MEP window area (including the added 10 ms for ipsilateral response) for the VL and TA was 52 ms and 40 ms respectively. A window of identical width was set prior to the stimulus artifact to measure background activity. Note the difference in the Y axis scales for the two muscles.

Figure 3. Average changes in normalized MEP areas for the VL (black bars) and TA (white bars) following anodal tDCS. Responses obtained from the target and non-target cortices are shown. ANOVA showed a significant effect of cortex, ***, $p < 0.001$. Vertical bars represent averages in each muscle and error bars are standard errors.

Figure 4.

Plot **A** represents the distribution of muscles that showed no modulation (I), inhibition of target cortex (II), facilitation of target and non-target cortex (III) and opposite sign modulation (IV). Plots **B**, **C** and **D** represent average changes in MEP window area following anodal tDCS. Each point represents individual subject data showing modulation of contralateral responses evoked from the target and non-target motor cortex. **B**, subjects who showed inhibition of responses from the target cortex (II). **C**, subjects who showed facilitation of responses from the target and non-target cortex (III). **D**, subjects who showed opposite sign modulation (facilitation of responses from the target cortex and inhibition of responses from the non-target cortex) (IV). Vertical bars represent averages within each group.

Figure 5.

Examples of rectified averaged EMG responses from the VL are shown for two representative subjects in whom ipsilateral connectivity was indicated (left panel) and ipsilateral connectivity was not indicated (right panel). Each panel has three sets of traces; the top set (A) shows contralateral responses with the coil preferentially positioned over the up-regulated hemisphere; the middle set (B) shows contralateral responses with the coil preferentially positioned over the down-regulated hemisphere; and the bottom set (C) shows ipsilateral responses with the coil preferentially positioned over the up-regulated hemisphere. Each EMG trace is an average of 15 MEPs showing pre-aTDCS (grey lines) and post-aTDCS (black lines) responses. Note the facilitation of ipsilateral responses in Example 1 and inhibition of ipsilateral responses in Example 2. Also note the low amplitude of background EMG due to the phase canceling that is inherent in trace averaging.