Cathodal transcranial direct current stimulation suppresses ipsilateral projections to presumed propriospinal neurons of the proximal upper limb

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Bradnam LV, Stinear CM, Byblow WD. Cathodal transcranial direct current stimulation suppresses ipsilateral projections to presumed propriospinal neurons of the proximal upper limb. J Neurophysiol 105: 2582–2589, 2011. First published March 9, 2011; doi:10.1152/jn.01084.2010.—This study investigated whether cathodal transcranial direct current stimulation (c-tDCS) of left primary motor cortex (M1) modulates excitability of ipsilateral propriospinal premotoneurons (PNs) in healthy humans. Transcranial magnetic stimulation (TMS) of the right motor cortex was used to obtain motor evoked potentials (MEPs) from the left biceps brachii (BB) while participants maintained contraction of the left BB. To examine presumed PN excitability, left BB MEPs were compared with those conditioned by median nerve stimulation (MNS) at the left elbow. Interstimulus intervals between TMS and MNS were set to produce summation at the C3–C4 level of the spinal cord. MNS facilitated BB MEPs elicited at TMS intensities near active motor threshold but inhibited BB MEPs at slightly higher intensities, indicative of putative PN modulation. c-tDCS suppressed the facilitatory and inhibitory effects of MNS. Sham tDCS did not alter either component. There was no effect of c-tDCS and sham tDCS on nonconditioned left BB MEPs or on the ipsilateral silent period of left BB. Right first dorsal interosseous MEPs were suppressed by c-tDCS. These results indicate that M1 c-tDCS can be used to modulate excitability of ipsilateral projections to presumed PNs controlling the proximal arm muscle BB. This technique may hold promise for promoting motor recovery of proximal upper limb function after stroke.

Therefore, input from both hemispheres ultimately determines task-specific selective muscle activation and formation of normal muscle synergies in the production of goal-directed upper limb movements such as reaching.

The propriospinal system can be studied indirectly in humans using single-pulse transcranial magnetic stimulation (TMS) combined with peripheral nerve stimulation. Using interstimulus intervals (ISIs) that permit summation at presumed C3–C4 PNs (e.g., Nicolas et al. 2001), combining a weak cortical stimulus with submotor threshold peripheral stimulation facilitates contralateral motor evoked potentials (MEPs). Conversely, a stronger cortical stimulus and the same peripheral stimulus suppresses MEPs, presumably due to the cortical stimulus recruiting higher threshold descending pathways reaching inhibitory interneurons within the spinal cord (Fig. 1; Iglesias et al. 2007; Nicolas et al. 2001; Roberts et al. 2008; Stinear and Byblow 2004b). The present study examined modulation of inputs from the ipsilateral hemisphere to presumed PNs during an upper limb task.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that can be used to transiently alter membrane potential of neuronal populations within primary motor cortex (M1), resulting in aftereffects that last several minutes. tDCS increases excitability when the anode is placed over M1, whereas with the cathode placed over M1, excitability is reduced (Lang et al. 2004; Nitsche and Paulus 2000, 2001; Nitsche et al. 2003a,b, 2005). Interestingly, there have been reports of enhanced ipsilateral arm function after cathodal tDCS (c-tDCS) in healthy humans (Vines et al. 2006) and enhanced paretic arm function in stroke patients after tDCS (Boggio et al. 2007; Fregni et al. 2005). c-tDCS has been shown to decrease excitability of uncrossed projections to ipsilateral proximal upper limb α-motoneurons (αMNs) (Bradnam et al. 2010b), which may explain observed effects on the ipsilateral arm. Improvements in function may also be due to reduced transcallosal inhibition from stimulated to nonstimulated hemisphere following c-tDCS (Schlaug et al. 2008; Williams et al. 2010).

The aim of the current study was to examine whether c-tDCS can indirectly downregulate presumed PNs and inhibitory interneurons intercalated in uncrossed pathways to the ipsilateral arm in healthy adults. Our hypothesis was that c-tDCS of left M1 would suppress ipsilateral descending inputs to PNs and inhibitory interneurons. The aftereffects of tDCS were examined on presumed PNs converging onto αMNs of the ipsilateral (left) biceps brachii (BB) by applying single-pulse TMS to right M1 in conjunction with median nerve stimulation (MNS) at the left elbow. c-tDCS of left M1 was...
compared with sham tDCS. In control experiments, MEPs were evoked from right first dorsal interosseous (FDI) as a manipulation check for effects of c-tDCS on left M1, and ipsilateral silent periods (iSPs) were evoked in left BB to assess effects of c-tDCS on transcallosal inhibition between hemispheres.

**METHODS**

**Ethical Approval**

The University of Auckland Human Participants Ethics Committee approved the study. All participants gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

**Participants**

Eighteen healthy adults (mean age $25 \pm 1.6$ y, range $19–50$ yr, 8 males) participated in the study following screening for contraindications to TMS by a neurologist. All participants were right-handed (range $+67$ to $+100$, mean $+81$), assessed by the Edinburgh Handnedness Inventory (Oldfield 1971).

**Electromyography**

Surface electromyography (EMG) was recorded from the long head of the right and left BB, just proximal to the musculotendinous junction at the elbow using disposable adhesive electrodes (30 × 20 mm; Ambu, Ballerup, Denmark) positioned 1 cm apart in a bipolar montage. EMG was recorded from the belly of the right and left FDI muscles. EMG was also recorded from left flexor carpi radialis (FCR) by electrodes positioned in a belly-tendon montage. EMG from electrodes positioned in a belly-tendon montage. EMG from FCR was only used to set the intensity for MNS; no data were collected or analyzed. EMG signals were amplified [CED 1902; Cambridge Electronic Design (CED), Cambridge, United Kingdom], band-pass-filtered (20–1,000 Hz), and sampled at 2 kHz (CED 1401).

**TMS**

Single-pulse TMS was delivered to the left and right M1 with a figure-of-8 coil (70-mm wing diameter; MagStim, Whitland, Dyfed, Wales). The handle of the coil was positioned posterolaterally at a 45° angle to induce a posterior-to-anterior current in the brain. The “hot spot” over right and left M1 for eliciting MEPs in contralateral BB were located and marked on the scalp. In right M1, active motor threshold (AMT) was determined as the minimum stimulus intensity that elicited a 100-μV MEP in 5 out of 10 trials during a left BB contraction. AMT was used to determine TMS intensities for eliciting left BB MEPs. During TMS, participants held a 450-g weight and maintained elbow flexion at 90°. This task was chosen to facilitate summation at the level of presumed BB PN (Burke et al. 1992; Mazevet and Pierrot-Deseilligny 1994; Nicolas et al. 2001). A range of TMS intensities were used, starting from AMT and increasing in 2% maximal stimulator output (MSO) steps, up to AMT + 8% MSO. The order of the intensities was randomized for each participant, and 16 nonconditioned MEPs and 16 MEPs conditioned by MNS were recorded in randomized order using Signal software (CED). Root mean square EMG (rmsEMG) was calculated between 100 and 10 ms prestimulus. Rest breaks were taken between trials to prevent fatigue.

To evoke iSPs in left BB, 12 stimuli were delivered to left M1 at 80% MSO using the same coil position and orientation as that for right BB MEPs. Eighty percent MSO was chosen, as thresholds to elicit iSPs are higher than those of MEPs (Chen et al. 2003; Trompetto et al. 2004). Stimuli were delivered at a rate of 0.2 Hz while participants performed an active left BB contraction while holding the same 450-g weight, with a rest between blocks of 4 stimuli. rmsEMG was calculated between 100 and 10 ms prestimulus.

**MNS**

Left MNS was delivered using a Digitimer DS7A constant current stimulator (Digitimer, Hertfordshire, United Kingdom). A 1-ms square-wave pulse was used to deliver the current via adhesive electrodes (Ambu) fixed over the median nerve at the elbow (cathode proximal). MNS intensity was set to 0.8 of motor threshold. This preferentially stimulates group I sensory afferents (Nicolas et al. 2001). An optimal range of ISIs between MNS and TMS was chosen to examine presumed PN modulation of αMNs located at the C5–C6 segment using methods described previously (Roberts et al. 2008). The efferent conduction time from M1 to C5–C6 (the location of αMNs for muscles in both experiments) was estimated as 6 ms, and the afferent conduction time from MNS to C5–C6 as 10 ms accounting for a 1-ms synapse onto the αMNs. Therefore, an ISI of 4 ms
would allow both stimuli to summate at BB αMNs. To assess interactions at presumed C3–C4 propriospinal interneurons, 3 ms was added (Pierrot-Deseilligny and Burke 2005). To account for individual variations in height/distance, ISIs ranging from 6 to 9 ms were initially examined in each subject using a TMS intensity of AMT + 2% MSO to optimize summation at the C3–C4 level (Roberts et al. 2008). The ISI that produced the greatest facilitation of left BB MEP was selected and used for the remainder of the experiment for that participant.

### Table 1. The experimental protocol

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre0</td>
<td>Conditioned and nonconditioned left BB MEPs</td>
</tr>
<tr>
<td>Pre20</td>
<td>Left BB iSPs</td>
</tr>
<tr>
<td>Pre22</td>
<td>Right FDI MEPs</td>
</tr>
<tr>
<td>Pre22</td>
<td>Left M1 c-tDCS or sham tDCS, 15 min, 1 mA (randomized order)</td>
</tr>
<tr>
<td>Post0</td>
<td>Rest</td>
</tr>
<tr>
<td>Post5</td>
<td>Conditioned and nonconditioned left BB MEPs</td>
</tr>
<tr>
<td>Post25</td>
<td>Left BB iSPs</td>
</tr>
<tr>
<td>Post27</td>
<td>Right FDI MEPs</td>
</tr>
</tbody>
</table>

BB, biceps brachii; MEPs, motor evoked potentials; iSPs, ipsilateral silent periods; FDI, 1st dorsal interosseous; M1, primary motor cortex; c-tDCS, cathodal transcranial direct current stimulation.

### Experimental Design and tDCS

Participants completed two experimental sessions, separated by 1 wk. The experimental protocol can be seen in Table 1. TMS measures were taken pre- and post-c-tDCS in each session. Either c-tDCS or sham tDCS was assigned to the session using a randomized and counterbalanced design. c-tDCS was delivered with a constant current of 1 mA for 15 min using a Phoresor II stimulator (Model PM850; IOMED) via two 35-cm² saline-soaked sponge electrodes, affixed to the scalp surface by compliant straps wrapped around the head. The cathode was positioned anterior and left of the vertex, at the hot spot for the right BB, also covering the hot spot of the right FDI. The anode was adhered to clean skin above the right supraorbital margin (Nitsche and Paulus 2000). The identical electrode configuration was used for sham tDCS, except the current was ramped down to 0 mA after 30 s (Gandiga et al. 2006). Participants sat quietly during the intervention and for 5 min following cessation of stimulation to consolidate effects.

### Data Processing and Analysis

MEPs in left BB. Left BB EMG was rectified, and the onset and offset latencies were used to calculate MEPAREA from each individual trace after subtracting background EMGAREA measured from an equivalent duration window for that trace (Bradnam et al. 2010b).

![Fig. 2. Averaged rectified left BB motor evoked potentials (MEPs) from 1 representative subject showing nonconditioned MEPs (left column) and conditioned MEPs (right column). Four TMS intensities were chosen relative to active motor threshold (AMT) to produce facilitation (FAC) and suppression (SUP; in this subject at AMT + 2% and AMT + 4%, respectively). The MEPAREA was calculated within the time window depicted between the dashed vertical lines. The ratio of the conditioned to nonconditioned MEPAREA (C/NC) is shown at the right (FAC > 1, SUP < 1). MSO, maximal stimulator output.](http://jn.physiology.org/doi/fig/10.1152/jn.00876.2010)
MEP\textsubscript{AREA} was then averaged and expressed as a conditioned-to-nonconditioned ratio (C/NC) at each intensity (AMT and AMT + 2, 4, 6, and 8% MSO). When combined with MNS, the TMS intensities required to produce maximum facilitation (FAC) and maximum suppression (SUP) of MEP\textsubscript{AREA} were identified for each participant. Left BB MEP ratios at the FAC and SUP intensities were analyzed using a 2 \text{STIMULATION} \times 2 \text{COMPONENT} \times 2 \text{TIME} \times 2 \text{CONDITION} \text{rmANOVA}. Left BB MEP ratios at intensities below FAC and above SUP were tested for effects of tDCS with paired \textit{t}-tests.

Nonconditioned left BB MEP\textsubscript{AREA} was tested for a difference between c-tDCS and sham tDCS at baseline using a paired \textit{t}-test. Post-tDCS, nonconditioned left BB MEP\textsubscript{AREA} was expressed as a percentage of pre-tDCS and tested with a 2 \text{STIMULATION} \times 2 \text{COMPONENT} \text{rmANOVA}.

rmsEMG for conditioned and nonconditioned traces was assessed with a 2 \text{STIMULATION} \times 2 \text{COMPONENT} \times 2 \text{TIME} \times 2 \text{CONDITION} \text{rmANOVA}.

MEPs in FDI. In all participants, MEPs in right FDI were elicited as a manipulation check for c-tDCS. MEP amplitude in right FDI was measured from 16 trials and then averaged. Baseline FDI MEP amplitude was compared with a paired \textit{t}-test. The post-tDCS amplitude was analyzed with a 1-sample \textit{t}-test to assess changes from baseline. A paired \textit{t}-test was used to assess the difference in FDI MEP amplitude between c-tDCS and sham tDCS. FDI prestimulus rmsEMG was analyzed using a 2 \text{STIMULATION} \times 2 \text{TIME} \text{rmANOVA}.

\textit{iSP}

Left BB traces were rectified and averaged for each participant. The \textit{iSP} onset was defined as when the poststimulus EMG fell continuously (for at least 10 ms) below the mean of the prestimulus EMG, in a window 30 – 60 ms after the stimulus. \textit{iSP} offset was defined as the time when EMG returned to baseline levels (Avanzino et al. 2007; Chen et al. 2003; Trompetto et al. 2004). The area between onset and offset points relative to the mean of the prestimulus rmsEMG was calculated (Giovannelli et al. 2009). Left BB \textit{iSP}\textsubscript{AREA} and rmsEMG were analyzed separately using a 2 \text{STIMULATION} \times 2 \text{TIME} \text{rmANOVA}.

\text{Significance level was set at } P < 0.05. \text{rmANOVAs were tested for } \text{sphericity and corrected where necessary. Post hoc } \textit{t}-\text{tests were used to explore main effects and interactions and were corrected for multiple comparisons (Rom 1990).}

\textbf{RESULTS}

\textit{Facilitation and Suppression of Left BB MEPs with MNS}

As predicted, MNS either facilitated or suppressed left BB MEP\textsubscript{AREA} in all participants and sessions, depending on the TMS intensity (Fig. 2). At low TMS intensities, conditioned MEPs were facilitated (FAC) relative to NC 31.5 ± 3.5 and 25.3 ± 3.1% for c-tDCS and sham sessions, respectively (both \(P < 0.001\); Fig. 3A). At higher TMS intensities, BB MEPs were suppressed by MNS. Conditioned MEP suppression Fig. 3. Left BB MEP ratios before (Pre; black bars) and after (Post; gray bars) cathodal transcranial direct current stimulation (c-tDCS) or sham tDCS. Each bar is the group average (\(n = 18\)). There were main effects of \text{COMPONENT} and interactions of \text{COMPONENT \times TIME} and \text{STIMULATION \times COMPONENT \times TIME}. A: before c-tDCS, conditioned MEPs were facilitated by MNS at TMS intensities near AMT (\(\dagger P < 0.001\)). c-tDCS attenuated the facilitation (\(\dagger P < 0.001\)). There was a difference in FAC after stimulation between conditions (\(\ast P < 0.05\)). B: before c-tDCS, conditioned MEPs were suppressed by MNS at higher TMS intensities (\(** P < 0.01\)). c-tDCS attenuated the suppression (\(\dagger P < 0.001\)). There was a difference in SUP after stimulation between conditions (\(\ast P < 0.05\)). Sham tDCS had no effect on either facilitation or suppression (both \(P > 0.08\)). C: left BB MEP ratios before (Pre; black bars) and after (Post; gray bars) c-tDCS to left M1 at 4 intensities relative to the intensity evoking left BB MEP facilitation. Each bar is the group average (\(n = 18\)). Note: FAC + 2% is the intensity for evoking left BB MEP suppression. There was no effect of c-tDCS at TMS intensities below FAC, indicating right M1 motor threshold was unchanged. Error bars indicate SE.
(SUP) relative to nonconditioned was $-14.7 \pm 2.5$ and $-10.8 \pm 2.9\%$ for c-tDCS and sham sessions, respectively (both $P < 0.01$; Fig. 3B).

**Left BB MEP Ratios**

There was a main effect of **COMPONENT** [$F_{(1,17)} = 118.92, P < 0.001$], a **COMPONENT \times TIME** interaction [$F_{(4,68)} = 36.96, P < 0.001$], and a **STIMULATION \times COMPONENT \times TIME** interaction [$F_{(2,34)} = 56.97, P < 0.001$]. Preintervention, there was no difference in MEP ratio between c-tDCS and sham tDCS sessions for either FAC ($P > 0.16$) or SUP ($P > 0.28$). For the FAC, paired $t$-tests revealed that BB MEP ratio was attenuated by c-tDCS (pre-, 31.5%; post-, 3.2%; $P < 0.001$) but not by sham tDCS (pre-, 25.3%; post-, 19.1%; $P > 0.15$; Fig. 3A). A paired $t$-test revealed a difference in FAC between c-tDCS and sham tDCS after stimulation ($P < 0.02$). One-sample $t$-tests showed that after tDCS the facilitation produced by MNS was abolished by c-tDCS ($P > 0.64$) but not sham ($P < 0.001$; Fig. 3A).

For SUP, paired $t$-tests revealed the inhibition was abolished by c-tDCS (pre-, $-14.7\%$; post-, $3.9\%; P < 0.001$). Sham tDCS had no effect on SUP (pre-, $-10.8\%$; post-, $-7.6\%; P = 0.08$). A paired $t$-test revealed a difference in SUP between c-tDCS and sham tDCS after stimulation ($P < 0.05$). One-sample $t$-tests showed that after tDCS, the inhibition produced by MNS was abolished by c-tDCS ($P > 0.43$) but not sham ($P < 0.01$; Fig. 3B). There were no other main effects or interactions (all $P > 0.061$).

There was no effect of c-tDCS on left BB MEP ratios at TMS intensities below FAC or above SUP (both $P > 0.15$; Fig. 3C).

There were no main effects or interactions for prestimulus rmsEMG (all $P > 0.27$). Average rmsEMG values were: c-tDCS, pre-, $0.024 \pm 0.004$ mV, post-, $0.025 \pm 0.003$ mV; and sham tDCS, pre-, $0.027 \pm 0.004$ mV, post-, $0.026 \pm 0.003$ mV.

**Nonconditioned Left BB MEPs**

Left BB nonconditioned MEP$_{\text{AREA}}$ are reported in Table 2. There were no main effects or interactions (all $P > 0.33$). There was no difference in nonconditioned BB MEP$_{\text{AREA}}$ between c-tDCS and sham tDCS at baseline ($P > 0.5$).

**Right FDI MEP Amplitude**

Right FDI MEP amplitude was suppressed by c-tDCS ($P < 0.05$). There was no difference in FDI MEP amplitude between c-tDCS and sham tDCS at baseline ($P > 0.4$). There was no effect of sham tDCS ($P = 0.35$). The paired $t$-test showed FDI MEP amplitude was suppressed by c-tDCS (pre-, $1.45 \pm 0.15$ mV; post-, $1.18 \pm 0.14$ mV) compared with sham tDCS (pre-, $1.58 \pm 0.22$ mV; post-, $1.64 \pm 0.26$ mV; $P < 0.05$; Fig. 4). There were no main effects or interactions for prestimulus rmsEMG (all $P > 0.44$). Average rmsEMG values were: c-tDCS, pre-, $0.009 \pm 0.001$ mV, post-, $0.010 \pm 0.001$ mV; and sham tDCS, pre-, $0.010 \pm 0.001$ mV, post-, $0.009 \pm 0.001$ mV.

**Left BB iSP**

iSPs occurred in 6 of 12 participants. There were no main effects or interactions for iSP$_{\text{AREA}}$ (all $P > 0.34$). There was no difference in left BB iSP$_{\text{AREA}}$ between c-tDCS and sham tDCS at baseline ($P > 0.9$). Average iSP$_{\text{AREA}}$ values were: c-tDCS, pre-, $0.101 \pm 0.022$ mV·ms, post-, $0.106 \pm 0.029$ mV·ms; and sham tDCS, pre-, $0.099 \pm 0.038$ mV·ms, post-, $0.074 \pm 0.035$ mV·ms. There were no main effects or interactions for left BB prestimulus rmsEMG from these trials (all $P > 0.41$). Average rmsEMG values were: c-tDCS, pre-, $0.020 \pm 0.004$ mV, post-, $0.021 \pm 0.005$ mV; and sham tDCS, pre-, $0.021 \pm 0.004$ mV, post-, $0.022 \pm 0.005$ mV.

**DISCUSSION**

In the present study, TMS and MNS were combined to examine presumed propriospinal modulation of BB αMNs. There was a facilitation of BB MEPs by MNS at low TMS intensities and suppression with higher intensities as observed previously (Iglesias et al. 2007; Nicolas et al. 2001; Roberts et al. 2008; Stinear and Byblow 2004b). The ISIs between peripheral stimulation and TMS are considered too long to affect the monosynaptic component of the MEP. We hypothesized that c-tDCS would reduce excitability of pathways projecting to presumed ipsilateral BB PNs, by modulation of direct projections to PNs (facilitation component), inhibitory interneurons to PNs (inhibitory component), or both. The main finding was that c-tDCS of left M1 suppressed both facilitation and inhibition of ipsilateral PNs, and to our knowledge this is the first demonstration that tDCS can affect the excitability of presumed propriospinal circuits. The putative mechanisms underlying these findings are discussed below.

**Suppression of Presumed Ipsilateral PNs by c-tDCS**

c-tDCS of left M1 reduced excitability of presumed PNs projecting to ipsilateral BB αMNs. The facilitation of left BB MEPs that occurred when MNS was combined with low-intensity TMS was abolished after c-tDCS. Furthermore, the inhibition of left BB MEPs that occurred when MNS was combined with higher intensity TMS was also abolished. Excitability of BB PNs and inhibitory interneurons was reduced following c-tDCS. There was no effect of sham tDCS on excitability of PNs or inhibitory interneurons. Right FDI MEPs

Table 2. Nonconditioned left BB MEP$_{\text{AREA}}$ at TMS intensities evoking MEP facilitation and suppression before and after c-tDCS and sham tDCS

<table>
<thead>
<tr>
<th>Component</th>
<th>c-tDCS</th>
<th>Sham tDCS</th>
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<tbody>
<tr>
<td><strong>Facilitation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1.02 ± 0.16</td>
<td>1.15 ± 0.23</td>
</tr>
<tr>
<td>Post</td>
<td>0.98 ± 0.18</td>
<td>1.12 ± 0.22</td>
</tr>
<tr>
<td><strong>Suppression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1.67 ± 0.32</td>
<td>1.58 ± 0.27</td>
</tr>
<tr>
<td>Post</td>
<td>1.72 ± 0.45</td>
<td>1.85 ± 0.42</td>
</tr>
</tbody>
</table>

Values are means ± SE. There were no significant findings (all $P < 0.33$). TMS, transcranial magnetic stimulation.
decreased in size after c-tDCS, suggestive of an overall suppressive effect of c-tDCS on left M1.

It is unlikely that interhemispheric modulation by c-tDCS can explain the current results. Nonconditioned MEPs in left BB did not increase after c-tDCS, as would be expected if right M1 was facilitated via interhemispheric projections (cf. Vines et al. 2006). iSPs in left BB were unaffected by c-tDCS, indicating transcallosal pathway excitability between left and right M1 was unchanged (Avanzino et al. 2007; Chen 2004; Chen et al. 2003, 2008; Meyer et al. 1995). These results should be interpreted bearing in mind that we only observed iSPs in half of our participants, perhaps because background muscle contraction was not sufficiently strong to evoke iSPs in all cases. In addition, interhemispheric inhibition may be mediated, in part, by mechanisms not reflected by the iSP (Chen et al. 2003). However, the aftereffects of c-tDCS, but not sham tDCS, on left BB MEP ratios at FAC and SUP further indicate that left M1 c-tDCS did not result from an increase in right M1 excitability. If right M1 excitability had increased, AMT would be lowered as a result, and presumed PNs would be facilitated and inhibited at slightly lower intensities. These effects were not observed (Fig. 3C), i.e., there was no evidence that the FAC and SUP components were shifted post-c-tDCS. Even given the interindividual variations in responses to c-tDCS, the magnitude of the overall effect at the lower intensity does not support a decrease in right M1 motor threshold.

There is growing evidence for a functionally important role of ipsilateral M1 in upper limb control in healthy humans (Bradnam et al. 2010a; Davare et al. 2007; Duque et al. 2008; Muellbacher et al. 2000; Perez and Cohen 2008). For example, ipsilateral M1 may contribute to task-specific selective muscle activation alongside contralateral M1 by maintaining the balance of excitation and inhibition over presumed PNs and αMNs (Bradnam et al. 2010a). This is particularly relevant in proximal muscles for which there are dense ipsilateral projections between M1 and spinal αMNs (Kuypers 1964; Lemon 2008). Robust representational areas are dedicated to proximal upper limb muscles in the PMC (He et al. 1993; Tanji et al. 1988). Secondary motor areas in the cat and nonhuman primate give rise to corticoreticular projections (Andrews et al. 1973; Catsman-Berrevoets and Kuypers 1976) that modulate excitability of inhibitory interneurons and PNs via the reticulospinal tract (Alstermark et al. 1984b,c; Illert et al. 1978, 1981). Our working hypothesis is that c-tDCS reduced excitation of presumed PNs and inhibitory interneurons via a reduction in excitability of the ipsilateral corticoreticulospinal descending pathway. Figure 5 illustrates schematically a simplified hypothetical circuit to explain this finding. The presumed C3–C4 PNs receive descending inputs from the contralateral corticospinal tract, forming a disynaptic projection to spinal αMNs (Gracies et al. 1994; Mazevet and Pierrot-Deseilligny 1994; Mazevet et al. 1996; Nicolas et al. 2001). In the cat and nonhuman primate, higher threshold cortical projections converge onto inhibitory interneurons, interposed with presumed PNs at C3–C4 (Alstermark et al. 1984a,b,c; Isa et al. 2006). A similar pattern of descending feedforward and feedback inhibition of presumed ipsilateral PNs is suggested in humans (Nicolas et al. 2001). PNs and inhibitory interneurons in the cat also receive inputs from the ipsilateral reticulospinal tract (Alstermark et al. 1984c; Illert et al. 1978, 1981). A similar...
pattern of reticulospinal convergence onto presumed PNs in humans would explain the current results. This finding may have implications for selective muscle activation and the formation of muscle synergies in the ipsilateral upper limb after M1 c-tDCS.

Potential Relevance for Upper Limb Control and Recovery After Stroke

Upper limb control is often impaired after stroke. Abnormal flexor synergies are common and impede functional recovery (Beer et al. 2007; Ellis et al. 2007; Sukal et al. 2007). It has been suggested that abnormal upper limb synergies arise after stroke, at least in part because of facilitated ipsilateral projections from contralesional M1 (Schwerin et al. 2008; Yao et al. 2009) and in part because of increased descending drive through presumed PNs (Mazevet et al. 2003; Stinear et al. 2004a). This pattern of ipsilateral upregulation may reflect compensation within the contralesional hemisphere for damage to the ipsilesional corticospinal tract (Bestmann et al. 2010; Lotze et al. 2006; Ward et al. 2003, 2006, 2007). Greater facilitation of ipsilateral PNs after stroke may overwhelm tonic PN inhibition, giving rise to abnormal muscle synergies (Pierrot-Deseilligny and Burke 2005). In future studies, c-tDCS of contralesional M1 may be a useful intervention to aid upper limb recovery in some patients after stroke, perhaps by reducing excitability of presumed ipsilateral PNs specifically. However, patients severely affected by stroke may rely on ipsilateral projections for remaining motor function, and this compensatory strategy may be compromised by contralesional M1 suppression. These ideas are speculative and require evaluation in a controlled trial but seem worthy of investigation.

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GRANTS

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DISCLOSURES

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

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