Task-Dependent Modulation of Inputs to Proximal Upper Limb Following Transcranial Direct Current Stimulation of Primary Motor Cortex

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Bradnam LV, Stinear CM, Lewis GN, Byblow WD. Task-dependent modulation of inputs to proximal upper limb following transcranial direct current stimulation of primary motor cortex. J Neurophysiol 103: 2382–2389, 2010. First published March 10, 2010; doi:10.1152/jn.01046.2009. Cathodal transcranial DC stimulation (c-tDCS) modulates activity in cortical projections to proximal and elbow (Dewald and Beer 2001; Dewald et al. 1995; Limb dysfunction is a problem for many stroke survivors, often on the hand (Nitsche et al. 2008). However, proximal upper limb dysfunction is unknown. This is an interesting question because proximal muscles are innervated by both contra- and ipsilateral inputs, such that output from one M1 projects bilaterally to motoneurons (MNs) innervating homologous muscles on either side of the body (Kuypers 1964; Lemon 2008; Palmer and Ashby 1992). tDCS may have the potential to modulate pathways that project ipsilaterally as well as contralaterally. In healthy adults, suppression of M1 by c-tDCS improved sequencing task performance by the contralateral hand but improved that of the ipsilateral hand (Vines et al. 2008), suggesting possible influences of c-tDCS on ipsilateral or interhemispheric pathways. Cathodal c-tDCS effects on proximal muscle M1 representations may also be modified by activation of the target muscle, as found for hand muscles (Thirunagasambandam et al. 2008).

The aim of this study was to determine the effects of c-tDCS of left M1 on corticomotor projections to infraspinatus (INF), a rotator cuff muscle important in shoulder joint stability and movement. We hypothesized that c-tDCS would suppress excitability of both the contra- and ipsilateral projections to INF bilaterally. The effects of c-tDCS on transcallosal inhibition were explored during uni- and bilateral INF contraction as these tasks may differentially alter transmission through transcallosal pathways (Stinear and Byblow 2004a,b).

METHODOLOGY

Participants

Fifteen healthy adults (age range: 19–48 yr, mean age: 31 ± 11 yr; 6 males) without history of upper limb neurological or musculoskeletal disorder completed the study. Participants were screened by a neurologist for contraindications to transcranial magnetic stimulation (TMS) and tDCS including epilepsy, head injury, metal implants, or CNS altering medications. All were right handed (range: +65 to +100, mean: +89) as assessed by the Edinburgh Handedness Inventory (Oldfield 1971). Informed consent was gained from all participants in accordance with the Declaration of Helsinki, and the study was approved by the local ethics committee.

Tasks

Upper limb tasks were used to preactivate INF during data collection because motor evoked potentials (MEPs) in proximal muscles cannot be evoked routinely without voluntary activation contralaterally (cMEPs) (Colebatch et al. 1990; Turton and Lemon 1999) and ipsilaterally (iMEPs) (Bawa et al. 2004; Lewis and Perreault 2007; Ziemann et al. 1999). Activation was also required to elicit ipsilateral silent periods (iSPs) (Avanzino et al. 2007; Chen 2003; Trompetto et al. 2004).

Participants were seated with their hands resting on their lap. In the bilateral condition, the participant moved their arms into full shoulder
external rotation and 70° of shoulder flexion, aligned to the plane of the scapula. The elbows were flexed to 90°, and the forearms were positioned midway between supination and pronation. In the left condition, participants moved the left arm to the same position while the right arm stayed at rest and vice versa during the right condition. cMEPs, iMEPs, and iSPs were collected from the target preactivated INF while participants maintained this position, so that INF was contracting isometrically to stabilize the shoulder joint at the time of stimulation (Barden et al. 2005; Itoi et al. 1994; Kronberg et al. 1990; Palmerud et al. 2000). Lifting the arm(s) to the same target position ensured there was a similar level of muscle contraction for each repetition. Movements were cued with an auditory metronome paced at 0.2 Hz, and the arms returned to the resting position between metronome beats. A schematic diagram of the motor tasks is presented in Fig. 1.

Electromyography

Surface electromyography (EMG) was recorded from the left and right INF via disposable adhesive electrodes (Ambu, Ballerup, Denmark) positioned 3 cm below the midpoint of the spine of the scapula and aligned with the direction of the underlying muscle fibers (Larsen et al. 1999). EMG was also recorded from right first dorsal interosseous (FDI), with electrodes placed over the muscle belly and the radial styloid process. EMG signals were amplified (CED 1902, Cambridge, UK), bandwidth filtered (20–1,000 Hz) and sampled at 2 kHz (CED 1401).

TMS

Single pulse TMS was delivered to the left M1 using a MagStim 200 magnetic stimulator (Dyfed, Wales). A figure eight coil (70 mm wing diameter) was positioned to induce a posterior to anterior current in the underlying tissues. The stimulation site evoking the largest TMS intensities [20–90% maximal stimulator output (MSO) in 10% increments] was applied to generate stimulus response curves during the three upper limb tasks. The bilateral task was used to elicit cMEPs in preactivated right INF, and iMEPs and iSPs in preactivated left INF (Fig. 1). During the bilateral task, cMEPs were also elicited in resting right FDI as a manipulation check to confirm that c-tDCS reduced the corticomotor excitability of this hand muscle representation. The left task was used to elicit iMEPs and iSPs in preactivated left INF along with cMEPs in the resting right INF. The right task was used to elicit cMEPs in preactivated right INF only. Stimulus intensity order was randomized, and six MEPs were evoked at a rate of 0.2 Hz at each intensity. Four stimulus-response curves were collected; pre-c-tDCS, immediately after c-tDCS (post 0), and 20 min (post 20) and 40 min (post 40) after c-tDCS. Bilateral, right, and left tasks were performed in a randomized order at each time point. The relatively small number of MEPs collected per stimulus intensity was restricted in part by the large range of intensities, number of tasks and time points.

tDCS

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 electrodes. The cathode, a saline soaked sponge, was positioned over the left M1 representation for the right INF and also covered the left M1 representation for the right FDI. The anode was a disposable self adhesive electrode (ViaSys) adhered to clean skin above the right supraorbital margin, in accordance with established protocols (Lang et al. 2004; Nitsche and Paulus 2000). Participants sat quietly during the intervention.

Data analysis

LEFT INF iMEPs. TMS of left M1 was used to evoke iMEPs in the activated left INF during the Left and Bilateral tasks. To determine iMEPs from background EMG activity, left INF EMG was rectified off-line using Signal software (CED, Cambridge, UK), then averaged and inspected for iMEPs between 10 and 30 ms poststimulus, similar to published protocols (Chen et al. 2003; Lewis and Perreault 2007). iMEPs were only evoked with stimulation intensities of 80 and 90% MSO, in 8 participants. Onset and offset latencies of the largest left INF iMEP were determined and used to calculate iMEPAREA for that participant (11–28 ms depending on the individual) (Fig. 2A). To account for any differences in background EMG, EMGAREA was calculated for each trial, in a window of prestimulus EMG equivalent in duration to that of the iMEPAREA analysis window, ending 0.1 ms before the stimulus. iMEP size was calculated for each trial, by subtracting background EMGAREA from the iMEPAREA using the formula: iMEP = (iMEPAREA – EMGAREA) × 1,000, where iMEPAREA is the area calculated between iMEP onset and offset latencies, EMGAREA is the background EMG area calculated over the same duration as the iMEPAREA, converted to mV.s. iMEPs were analyzed with a repeated measures ANOVA (rmANOVA) with factors intensity (80%, 90%), task (bilateral, left) and time (pre, post 0, post 20, post 40). There was no effect of, or any interaction with, intensity (all P > 0.31). Therefore iMEPs were averaged across 80 and 90% MSO as an

FIG. 1. A schematic diagram of the posterior view of participants performing the motor tasks used for preactivation of infraspinatus (INF) for transcranial magnetic stimulation (TMS). The main results are summarized under each figure. \( \downarrow \) smaller left INF ipsilateral motor evoked potentials (iMEPs), ipsilateral silent periods (iSPs), and right INF contralateral MEPs (cMEPs), \( \approx \) no significant change following cathodal transcranial DC stimulation (c-tDCS).
in all participants at both 80 and 90% MSO, iSPAREA were averaged
pants and at 70% MSO in 10 participants. Because iSPs were present
earlier studies in hand muscles (Chen et al. 2003; Netz et al. 1997;
elicited at lower stimulus intensities than iMEPs in agreement with
B
). Ipsilateral SPs were
first time when EMG returned to baseline (Avanzino et al. 2007; Chen
20 – 60 ms after the stimulus. Ipsilateral SP offset was defined as the
5 ms) below the mean of the prestimulus EMG, in a window
defined as the time when the poststimulus EMG fell continuously (for
indicating c-tDCS had suppressed FDI cMEPs as in previous reports
(e.g., Lang et al. 2004). FDI cMEPs were reduced compared with
baseline at 50% MSO and above at post 0 and at 90% MSO at post 20
and post 40 (all \( P < 0.04 \)) (Fig. 3), confirming that the effects of the
c-tDCS were comparable to those observed in earlier studies of distal
hand muscles.

The level of significance for all statistical tests was set at \( P < 0.05 \).
Multiple ANOVAs were performed to explore main effects and
interactions. These were not corrected. Paired \( t \)-tests were used to
explore significant main effects and interactions. Two-tailed, one
sample \( t \)-tests were used to test whether percent change scores
differed from unity. All post hoc tests were corrected for multiple
comparisons (Rom 1990). Means ± SE are reported in the text.

R E S U L T S

The main results are summarized in Table 1. c-tDCS de-
creased left INF iMEPs and right INF cMEPs in the left task
only. In contrast, the left INF iSP was attenuated in both left
and bilateral tasks.

L E F T  I N F  i S P s

TMS of left M1 was used to elicit iSPs in the activated
left INF during the left and bilateral tasks. Left INF iSPAREA was
calculated from the rectified averaged traces to measure the effects of
c-tDCS on transcallosal inhibition (TCI). Ipsilateral SP onset was
defined as the time when the poststimulus EMG fell continuously (for
\( \geq 10 \) ms) below the mean of the prestimulus EMG, in a window
20–60 ms after the stimulus. Ipsilateral SP offset was defined as the
first time when EMG returned to baseline (Avanzino et al. 2007; Chen
et al. 2003; Trompetto et al. 2004) (Fig. 2B). Ipsilateral SPs were eli-
cited at lower stimulus intensities than iMEPs in agreement with
earlier studies in hand muscles (Chen et al. 2003; Netz et al. 1997;
Wassermann et al. 1994). At 60% MSO iSPs occurred in 7 partici-
pants and at 70% MSO in 10 participants. Because iSPs were present
in all participants at both 80 and 90% MSO, iSPAREA were averaged
across these two intensities as for left INF iMEPs.

Ipsilateral MEPs, SPs, and rmsEMG were analyzed separately
using a two task (bilateral, left) times four time (pre, post 0, post 20,
post 40) rmANOVA. The change in iMEPAREA post-tDCS was also
analyzed using a two task (bilateral, left) times three time (pre 0,
post 20, post 40) rmANOVA. As a manipulation check, cMEPs were
obtained in the resting right FDI during the bilateral condition. These
data were analyzed in a four time (Pre, post 0, post 20, post 40) times
eight intensity (20–90% MSO) rmANOVA. There was a main effect of task
(\( P < 0.01 \)), as cMEPs were larger when right INF was preactivated (bilateral)
compared with rest (left).

The main effects of task and time, post-c-tDCS cMEP area was
expressed as percent change from pre-tDCS as for INF iMEPs, and
analyzed using a two task (bilateral, left) times three time (post 0, post
20, post 40) rmANOVA. rmsEMG during bilateral and left tasks was
analyzed separately as described in the preceding text at intensities of
80 and 90% MSO.

TMS of left M1 was used to elicit cMEPs in the activated
right INF during the right and bilateral tasks and in the resting right
INF during the left task. Right INF EMG was rectified off-line, then averaged
for each stimulation intensity. Area of the contralateral MEP (cME-
PAREA) was calculated from the average trace at each intensity, from
the onset latency to the first point where EMG returned to baseline
following the cMEP peak (9–25 ms depending on the individual).
Background EMGAREA was subtracted from cMEPAREA using
the same formula as for iMEPs.

A number of comparisons were made to determine the task-
dependent effects of c-tDCS on right INF corticomotor excitability.
Right INF cMEPs were analyzed during unilateral (right task) activi-
tation, compared between uni- and bilateral activation (right and
bilateral tasks), and compared between bilateral activation and rest
(bilateral and left tasks).

Stimulus-response curves from the bilateral task were normalized for
each individual by expressing the mean INF cMEPAREA at each stimulus
intensity as a proportion of the maximal mean INF cMEPAREA, rmsEMG
was calculated between 100 and 1 ms prior to the stimulus and averaged.
Right INF cMEPAREA and rmsEMG were analyzed separately using a
four time (pre, post 0, post 20, post 40) times eight intensity (20–90%
MSO) rmANOVA.

To assess the effects of c-tDCS on voluntarily activated right
INF, cMEPs and rmsEMG were analyzed separately using two task (right,
bilateral) times four time (pre, post 0, post 20, post 40) times three
intensity (40, 50, 60% MSO) rmANOVA. These three stimulation
intensities were analyzed as they were common to both tasks.

To compare the effects of c-tDCS on resting and activated right
INF, cMEPAREA was analyzed with a rmANOVA with factors inten-
sity (80, 90%), task (bilateral, left), and time (pre, post 0, post 20, post
40). The analysis was confined to these stimulus intensities as they
elicited cMEPs from the resting right INF in 10 participants. There
was no effect of, or any interaction with, intensity (all \( P > 0.12 \)),
therefore cMEPs at the two intensities were averaged as for iMEPs.

There was a main effect of task (\( P < 0.01 \)), as cMEPs were larger
when right INF was preactivated (bilateral) compared with rest (left).
To explore the effects of task and time, post-c-tDCS cMEP area was
expressed as percent change from pre-tDCS as for INF iMEPs, and
analyzed using a two task (bilateral, left) times three time (post 0, post
20, post 40) rmANOVA. rmsEMG during bilateral and left tasks was
analyzed separately as described in the preceding text at intensities of
80 and 90% MSO.
bilateral and left tasks. In two participants, iMEPs were present after, but not before, c-tDCS. Mean iMEP onset latency was 13.6 ± 2.1 ms. Cathodal tDCS caused task dependent changes in left INF iMEP area in the eight participants who exhibited iMEPs pre- or post-c-tDCS. There was no main effect of task or time (both \( P > 0.43 \)); however, there was a task by time interaction \( [F(3,5) = 3.80, P < 0.05; \text{Fig. 4A}] \). Left INF iMEPs were smaller at post 20 in the left task than the bilateral task \( (P = 0.041) \). There was no effect of task at pre, post 0, or post 40 (all \( P > 0.18 \)). For rmsEMG, there were no main effects or an interaction (all \( P > 0.18 \)) (Table 2). Post-c-tDCS iMEP area was also expressed as percent change in the six participants with iMEPs pre-c-tDCS. In this cohort, there was no main effect of task or time (both \( P > 0.18 \)). There was a task by time interaction \( [F(2,4) = 6.25, P < 0.05] \), left INF iMEP area was reduced at post 20 by 41% after c-tDCS in the left task \( (P = 0.047; \text{Fig. 4B}) \).

**Left INF iSPs**

Ipsilateral SPs were identified in all 15 participants. There was a main effect of time \( [F(3,12) = 3.35, P < 0.05] \). Paired \( t \)-test found a reduction in the mean iSP\(_{\text{AREA}}\) compared with pre and at post 0 \( (P = 0.006) \) and at post 20 \( (P = 0.015) \) but not at post 40 \( (P > 0.20; \text{Fig. 5}) \). There was no main effect of task or interaction between task and time (both \( P > 0.5 \)).

**Right INF cMEPs**

Right INF cMEPs were evoked in all participants prior to c-tDCS in the active tasks. Mean onset latency of right INF cMEPs was 10.1 ± 1.4 ms. At rest (left task), right INF cMEPs could be evoked in 10 participants prior to c-tDCS. In no cases were right INF cMEPs present only after c-tDCS in the left task. The effects of c-tDCS on right INF cMEPs were task-dependent as indicated in two separate analyses.

**TABLE 1. Summary of significant results**

<table>
<thead>
<tr>
<th>Tasks</th>
<th>ANOVA</th>
<th>TMS Intensities (%MSO)</th>
<th>( n )</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left INF iMEPs</td>
<td>Bilateral, Left</td>
<td>2 task × 4 time</td>
<td>80, 90 (averaged)</td>
<td>8 task × time (0.037)</td>
</tr>
<tr>
<td></td>
<td>Bilateral, Left</td>
<td>2 task × 3 time</td>
<td>80, 90 (averaged)</td>
<td>6 task × time (0.041)</td>
</tr>
<tr>
<td>Left INF iSPs</td>
<td>Bilateral, Left</td>
<td>2 task × 4 time</td>
<td>80, 90 (averaged)</td>
<td>15 time (0.028)</td>
</tr>
<tr>
<td>Right INF cMEPs</td>
<td>Bilateral, Left</td>
<td>2 task × 3 time</td>
<td>80, 90 (averaged)</td>
<td>10 task (0.033)</td>
</tr>
<tr>
<td>Right INF cMEP S-R curve</td>
<td>Bilateral, Right</td>
<td>2 task × 4 time × 3 intensity</td>
<td>40, 50, 60 (averaged)</td>
<td>15 intensity (0.001)</td>
</tr>
<tr>
<td>Right FDI cMEP S-R curve</td>
<td>Bilateral, Right</td>
<td>4 task × 8 intensity</td>
<td>20–90 (10% increments)</td>
<td>15 intensity (0.001)</td>
</tr>
<tr>
<td></td>
<td>Bilateral, Right</td>
<td>4 task × 8 intensity</td>
<td>20–90 (10% increments)</td>
<td>14 time (0.010) intensity (0.001)</td>
</tr>
</tbody>
</table>

\(P\) values, in parentheses, have not been corrected for multiple comparisons. TMS, transcranial magnetic stimulation; INF, infraspinatus; iMEP and cMEP, ipsi- and contralateral motor evoked potential, respectively; iSP, ipsilateral silent period; S-R, stimulus response; FDI, First dossal interosseous.
The first analysis compared the effects of c-tDCS on right INF cMEPs recorded with the muscle at rest (left task) and voluntarily activated (bilateral task) in the 10 participants with cMEPs at rest. Comparison of cMEP percent change between left and bilateral tasks showed a task \times time interaction \(F(2,8) = 4.13, P < 0.05\). There were no main effects (both \(P > 0.28\)). The effects of c-tDCS on cMEP area differed between the left and bilateral tasks at post 20 (\(P = 0.013\)) due to a 26% reduction of cMEP area in left task (\(P = 0.029\)) (Fig. 6A). There were no main effects of time, intensity, or any interactions (all \(P > 0.14\)) for right INF rmsEMG (Table 2).

Comparison of right INF cMEPs in bilateral and right tasks was performed for three intensities of stimulation in all 15 participants. There was a main effect of intensity \(F(2,13) = 16.35, P < 0.001\) but no main effect of task or time or an interaction between time and intensity (both \(P > 0.14\)) on cMEP area (Fig. 6B). Background EMG was consistent with no main effects or interactions (all \(P > 0.2\)).

**DISCUSSION**

This study investigated the effects of left M1 c-tDCS on corticospinal and transcallosal projections serving the left and right INF muscles in healthy humans performing uni- and bilateral motor tasks. There were two novel findings. The first was task-dependent effects on left INF iMEPs and right INF cMEPs, which were both suppressed after c-tDCS during the left task only. The second novel finding was that the iSP in left INF was suppressed after c-tDCS in both the left and bilateral tasks, suggesting a reduction of transcallosal inhibition from left to right M1, independent of task.

**Infraspinatus MEPs**

Contralateral MEPs in right INF were easily elicited in all participants when the muscle was preactivated during bilateral and right tasks. In contrast, high thresholds at rest made it difficult to evoke cMEPs even with strong stimulation during TABLE 2. **rmsEMG values for left and right INF during bilateral and unilateral motor tasks**

<table>
<thead>
<tr>
<th></th>
<th>Unilateral Task</th>
<th>Bilateral Task</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post 0</td>
</tr>
<tr>
<td>Left INF</td>
<td>0.029 ± 0.003</td>
<td>0.027 ± 0.003</td>
</tr>
<tr>
<td>Right INF*</td>
<td>0.041 ± 0.007</td>
<td>0.040 ± 0.006</td>
</tr>
<tr>
<td>Right INF**</td>
<td>0.009 ± 0.001</td>
<td>0.009 ± 0.001</td>
</tr>
</tbody>
</table>

Values are means ± SE in millivolts. RMS EMG, root mean square electromyography. *Right task. **Left task.

**FIG. 6.** A: right INF cMEP percent difference from pre-t-DCS at post 0, post 20, and post 40 during bilateral (●) and left conditions (▲). Each bar is the group average (n = 10). There was cMEP suppression at post 20 (*\(P < 0.05\)) in the left task. Error bars indicate SE. B: average normalized stimulus-response curves for right INF at pre, post 0, post 20, and post 40 (n = 15). Error bars indicate SE.
the left task. High rest motor thresholds in contralateral INF are consistent with those described in other proximal upper limb muscles (Colebatch et al. 1990; Schieppati et al. 1996; Turton and Lemon 1999).

Left INF iMEPs were identified in about half of the participants, a proportion similar to previous findings in healthy adults (Lewis and Perreault 2007; Misawa et al. 2008). The average onset latency for iMEPs was 3.5 ms longer than cMEPs, also in line with previous studies involving proximal musculature (Alexander et al. 2007; Bawa et al. 2004; Caramia et al. 2000; Chen et al. 2003; MacKinnon et al. 2004; Misawa et al. 2008; Ziemann et al. 1999). The longer latency of iMEPs may reflect activation of indirect cortico-reticulospinal or cortico-proprio-spinal pathways rather than uncrossed corticospinal projections (Ziemann et al. 1999).

**Task-dependent effects on INF MEPs**

Cathodal tDCS of left M1 suppressed contralateral and ipsilateral projections during the left task. However, there was no suppression of left INF iMEPs during the bilateral task or of right INF cMEPs in bilateral or right tasks. To our knowledge, this is the first report that c-tDCS can alter activity in contralateral and ipsilateral pathways to a proximal upper limb muscle in a task-dependent manner. The absence of MEP suppression during right and bilateral tasks may have resulted from right INF muscle activity counterevoking the suppressive effects of c-tDCS on contralateral projections as found previously in studies examining c-tDCS effects on hand motor cortex (Galea and Celnik 2009; Thirugnanasambandam et al. 2008). Similarly, performance of repetitive contralateral hand muscle contractions before or after inhibitory rTMS can reverse the suppressive effect on M1 (Gentner et al. 2008; Huang et al. 2008; Iezzi et al. 2008). This “overriding” of inhibitory brain stimulation by motor practice may also occur in contralateral proximal muscles, explaining the current pattern of results in right and bilateral tasks. Another consideration is the nature of the task itself. Cathodal tDCS (in contrast to anodal tDCS) appears to have little influence on motor or visual-motor learning, or on the formation of motor memory (Antal et al. 2004; Galea and Celnik 2009; Nitsche et al. 2003b; Reis et al. 2009). The choice of motor training task might be a critical factor in determining the outcome of brain stimulation therapies (Bolognini et al. 2009), but further work is required to support this idea.

Our finding that c-tDCS altered excitability of ipsilateral projections is consistent with previous work demonstrating c-tDCS and inhibitory rTMS over hand motor cortex alters ipsilateral hand function. However, some studies have shown ipsilateral hand performance is reduced (Carey et al. 2006; Chen et al. 1997) whereas others have found it enhanced (Avanzino et al. 2008; Dafoятis et al. 2008; Kobayashi et al. 2004, 2009; Vines et al. 2008). Further investigation is required to elucidate whether a reduction in iMEPs (unimanual task) or an increase in iMEPs (bilateral task) in the left INF after c-tDCS would promote better function in the ipsilateral proximal limb.

M1 c-tDCS may have also affected premotor cortex, given the size and location of the stimulating cathode. Anodal tDCS over dorsal premotor cortex can alter excitability of intracortical circuits within ipsilateral M1 (Boros et al. 2008). The representation of proximal muscles relative to distal muscles is greater in dorsal premotor cortex than in M1 (Dum and Strick 1991). Therefore we cannot rule out the possibility that influences originating within dorsal premotor cortex may have given rise, in part, to the current pattern of results; however, this could not explain the task-dependent modulation of iMEPs and cMEPs.

**iSPs**

c-tDCS suppressed iSPs immediately, and for ≥20 min after stimulation in left and bilateral tasks, indicating reduced transcallosal inhibition from left to right M1. The iSP is a TMS-induced EMG suppression thought to reflect, in part, activation of transcallosal pathways in the stimulated hemisphere that inhibit ongoing activity in the contralateral hemisphere (Trompetto et al. 2004). The iSP has been used as an indication of transcallosal pathway integrity and excitability (Avanzino et al. 2007; Chen et al. 2003; Reis et al. 2008; Trompetto et al. 2004). Unlike the task-dependent effects of c-tDCS on iMEPs and cMEPs, there was no effect of task on the iSP. Reduced TCI in the left task is consistent with the pattern of results for iMEPs and cMEPs, pointing to c-tDCS suppression of outputs from left M1 during this task. In contrast, during the bilateral task TCI may have been suppressed by the task itself because upper limb bimanual mirror movements reduce TCI between homologous muscle representations (Stinear and Byblow 2004a,b).

Our results differ to those of Lang et al. (2004), who found no change in left FDI iSP after 10 min of c-tDCS of the left M1. The authors suggested this may have arisen by use of a stimulation intensity (1 mA) that was too weak to modulate higher threshold TCI pathways. TDCS was applied for 15 min in the present study, and this may have been more efficacious. The difference in findings between the two studies may also lie in the disparity in strength of TCI (Harris-Love et al. 2007) between proximal and distal arm muscle homologous representations. Further experiments are required to resolve these, or alternative, possibilities.

**Time course of c-tDCS aftereffects**

In the left task, cMEPs and iMEPs were unchanged immediately following c-tDCS (post 0) and were significantly reduced at 20 min. While aftereffects were still apparent at 40 min poststimulation, the difference from baseline was not significant. The delayed onset of cMEP suppression is similar to previous studies. In one, c-tDCS effects were not evident until eleven minutes after stimulation and had dissipated after 40 min (Priori 2003). In others, suppressive rTMS neurophysiological and behavioral effects were delayed after stimulation by ≥2 min (Carey et al. 2006; Romero et al. 2002). Together these results may indicate a temporal requirement for summation of inputs within M1 that delay the observed effect (Carey et al. 2006). In contrast, iSPs in the left INF were significantly attenuated immediately and at 20 min after c-tDCS. The difference in onset of suppression between MEPs and iSPs may be related to the different populations of neurons comprising corticospinal and transcallosal pathways (Lee et al. 2007). The stimulation intensity for evoking iSPs is lower than that required to elicit iMEPs and cMEPs in INF as we observed and
Clinical implications
The current findings suggest that the suppressive effects of M1 c-tDCS on proximal musculature are observable during unimanual activity of the ipsilateral upper limb, but not during unimanual activity of the contralateral upper limb, or bimanual activity. This may have implications for the use of tDCS during upper limb rehabilitation after stroke (Hummel and Cohen 2006). After stroke, imbalanced M1 excitability occurs due to reduced inhibition from the ipsi- to contrallosal hemisphere and contributes to impaired upper limb function (Butefisch et al. 2008; Liepert et al. 2000; Manganotti et al. 2002, 2008; Murase et al. 2004; Netz et al. 1997; Shimizu et al. 2002; Stinear et al. 2008). In chronic stroke patients, contralosal M1 c-tDCS improves paretic hand function in some cases (Boggio et al. 2007; Fregni et al. 2005), and in studies involving healthy participants, skilled function of the ipsilateral hand has improved after c-tDCS or repetitive TMS (rTMS) (Avanzino et al. 2008; Dafotakis et al. 2008; Kobayashi et al. 2004, 2009; Vines et al. 2008). In the present study, c-tDCS reduced the excitability of contralateral, ipsilateral, and interhemispheric projections originating from proximal muscle representations within the stimulated M1 in a task-dependent manner. This may be usefully applied to the contralosal M1 to promote re-balancing of cortical excitability, and this may improve functional outcomes in proximal upper limb as has been shown for hand muscles (Stinear et al. 2008; Traversa et al. 1998; Vines et al. 2008). However, the present results suggest that contralosal c-tDCS and voluntary motor activity confined to the ipsilateral (paretic) upper limb have the opposite effect on ipsilateral excitability when compared with bilateral movements. The most effective mode of motor practice requires further investigation before c-tDCS is used as an adjunct to proximal upper limb rehabilitation following stroke.

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References


