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

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Abstract

This study investigated whether cathodal transcranial direct current stimulation (c-tDCS) of left primary motor cortex (M1) modulates excitability of ipsilateral propriospinal pre-motoneurons (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 to those conditioned by median nerve stimulation (MNS) at the left elbow. Interstimulus intervals between TMS and MNS were set to produce summation at the C3-4 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. Cathodal tDCS suppressed the facilitatory and inhibitory effects of MNS. Sham c-tDCS did not alter either component. There was no effect of c-tDCS and sham tDCS on non-conditioned left BB MEPs, or on the ipsilateral silent period of left BB. Right first dorsal interosseous (FDI) 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.
Introduction

Propriospinal neurons (PNs) located in the 3rd and 4th segments in the spinal cord (C3-C4) mediate descending commands for target reaching in the cat and non-human primate (Alstermark et al., 2007). Also known as cervical “pre-motoneurons”, presumed PNs integrate sensory feedback with descending cortical output to rapidly update the motor command during a reaching task (Pierrot-Deseilligny & Burke, 2005). In human and non-human primates, PNs are held under tonic suppression (Pierrot-Deseilligny, 1996; Pierrot-Deseilligny & Burke, 2005; Isa et al., 2006; Alstermark et al., 2007) that is released during activities requiring co-contraction of proximal and distal upper limb muscles (Nicolas et al., 2001; Iglesias et al., 2007; Roberts et al., 2008). As such, PNs facilitate the formation of muscle synergies (Pierrot-Deseilligny & Burke, 2005). Interestingly, descending inputs to presumed PNs originate in both the contralateral hemisphere (Mazevet et al., 1996; Nicolas et al., 2001; Boudrias et al., 2010) and ipsilateral hemisphere via the reticulospinal tract (Illert et al., 1981; Illert et al., 1978). 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 that permit summation at presumed C3-C4 PNs (e.g., Nicolas et al., 2001), combining a weak cortical stimulus with sub-motor 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.
(Figure 1; Nicolas et al., 2001; Stinear & Byblow, 2004b; Iglesias et al., 2007; Roberts et al., 2008). 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 non-invasive brain stimulation technique that can be used to transiently alter membrane potential of neuronal populations within M1, resulting in after-effects that last several minutes. tDCS increases excitability when the anode is placed over M1, whereas with the cathode placed over M1, excitability is reduced (Nitsche & Paulus, 2000, 2001; Nitsche et al., 2003a; Nitsche et al., 2003b; Lang et al., 2004; Nitsche et al., 2005). Interestingly there have been reports of enhanced ipsilateral arm function after cathodal tDCSs (c-tDCS) in healthy humans (Vines et al., 2006), and enhanced paretic arm function in stroke patients after tDCS (Fregni et al. 2005; Boggio et al. 2007). c-tDCS has been shown to decrease excitability of uncrossed projections to ipsilateral proximal upper limb 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 non-stimulated hemisphere following c-tDCS (Schlaug et al. 2008; Williams et al., 2010).

This aim of the current study was to examine whether c-tDCS can indirectly down-regulate 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 after-effects of tDCS were examined on presumed PNs converging onto alpha motoneurons (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. Cathodal tDCS of left M1 was compared with sham tDCS. In control experiments, MEPs were evoked from right 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 (UAPEC) 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 ± 1.6 yr, 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 Handedness 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 x 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 FCR was only used to set the intensity for MNS, no data were collected or analysed. EMG
Signals were amplified (CED 1902, Cambridge, UK), bandpass filtered (20 – 1000 Hz) and sampled at 2 kHz (CED 1401, Cambridge, UK).

Transcranial Magnetic Stimulation

Single-pulse TMS was delivered to the left and right M1 with a figure-of-eight coil (70 mm wing diameter), (MagStim Co., 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 ‘hotspot’ 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 five out of ten 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 PNs (Burke et al., 1992; Mazevet & 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 randomised for each participant and sixteen non-conditioned MEPs and sixteen MEPs conditioned by MNS were recorded in randomised order using Signal software (CED, Cambridge UK). Root mean square EMG (rmsEMG) was calculated between 100 - 10 ms pre-stimulus. Rest breaks were taken between trials to prevent fatigue.

To evoke ipsilateral silent periods (iSPs) in left BB, twelve stimuli were delivered to left M1 at 80% MSO using the same coil position and orientation as that for right BB MEPs. 80% 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 450g weight, with a rest between blocks of four stimuli. rmsEMG was calculated between 100 - 10 ms pre-stimulus.

**Median Nerve Stimulation**

Left median nerve stimulation (MNS) was delivered using a Digitimer DS7A constant current stimulator (Digitimer, Hertfordshire, UK). A 1 ms square wave pulse was used to deliver the current via adhesive electrodes (Ambu, Ballerup, Denmark) 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 interstimulus intervals (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 - 9 ms was initially examined in each subject using a TMS intensity of AMT + 2% MSO, to optimise 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.
Experimental design and transcranial direct current stimulation

Participants completed two experimental sessions, separated by one week. 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. Cathodal t-DCS was delivered with a constant current of 1 mA for 15 min using a Phoresor® II stimulator (Model PM850, IOMED Inc., Utah) 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 hotspot for the right BB, also covering the hotspot of the right FDI. The anode was adhered to clean skin above the right supraorbital margin (Nitsche & 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 five minutes 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 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). MEPAREA was then averaged and expressed as a ratio (C/NC) at each intensity (AMT, AMT + 2, 4, 6, 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 analysed using a 2 \textit{STIMULATION} (c-tDCS, sham tDCS) x 2
\textit{COMPONENT} (FAC, SUP) x 2 \textit{TIME} (Pre, Post) repeated measures ANOVA (rmANOVA). Left
BB MEP ratios at intensities below FAC and above SUP were tested for effects of tDCS with
paired t-tests.

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

Root mean squared EMG (rmsEMG) for conditioned and non-conditioned traces was
assessed with a 2 \textit{STIMULATION} x 2 \textit{COMPONENT} x 2 \textit{TIME} x 2 \textit{CONDITION} (NC, C) rmANOVA.

\textbf{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 sixteen trials then averaged. Baseline FDI MEP
amplitude was compared with a paired-test. The post-tDCS amplitude expressed as a percentage
of pre-tDCS MEP amplitude. Right FDI MEP amplitude was analysed with a one-sample t-test
to assess changes from baseline. A paired t-test was used to assess the difference in FDI MEP
amplitude between c-tDCS and sham tDCS. FDI pre-stimulus rmsEMG was analysed using a 2
\textit{STIMULATION} x 2 \textit{TIME} rmANOVA.
Ipsilateral Silent Period (iSP)

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

Significance level was set at $P < 0.05$. Repeated measures ANOVAs were tested for sphericity and corrected where necessary. Post hoc t-tests were used to explore main effects and interactions, and were corrected for multiple comparisons (Rom, 1990).

Results

Facilitation and Suppression of left BB MEPs with MNS

As predicted, MNS either facilitated or suppressed left BB MEP_{AREA} in all participants and sessions, depending on the TMS intensity (Figure 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 $P < 0.001$) (Figure 3a). At higher TMS intensities BB MEPs were suppressed by MNS. Conditioned MEP suppression (SUP) relative to non-conditioned was -14.7 ± 2.5% and -10.8 ± 2.9% for c-tDCS and sham sessions respectively (both $P < 0.01$) (Figure 3b).
Left BB MEP ratios

There was a main effect of COMPONENT $[F_{(1,17)} = 118.92, P < 0.001]$, a COMPONENT x TIME interaction $[F_{(1,17)} = 36.96, P < 0.001]$ and a STIMULATION x COMPONENT x TIME interaction $[F_{(1,17)} = 56.97, P < 0.001]$. Pre-intervention, 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%, $P > 0.15$) (Figure 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 ($P < 0.001$) (Figure 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 ($P < 0.01$) (Figure 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 $P > 0.15$) (Figure 3c).

There were no main effects or interactions for pre-stimulus rmsEMG (all $P > 0.27$).

Average rmsEMG values were: c-tDCS pre 0.024 ± 0.004 mV, post 0.025 ± 0.003 mV and sham tDCS, pre 0.027 ± 0.004 mV, post 0.026 ± 0.003 mV.
Non-conditioned left BB MEPs

Left BB non-conditioned MEP\textsubscript{AREA} are reported in Table 2. There were no main effects or interactions (all $P > 0.33$). There was no difference in non-conditioned BB MEP\textsubscript{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 ± 0.15 mV, post 1.18 ± 0.14 mV) compared to sham tDCS (pre 1.58 ± 0.22 mV, post 1.64 ± 0.26 mV) ($P < 0.05$) (Figure 4). There were no main effects or interactions for pre-stimulus rmsEMG (all $P > 0.44$). Average rmsEMG values were: c-tDCS, pre 0.009 ± 0.001 mV, post 0.010 ± 0.001 mV and sham tDCS, pre 0.010 ± 0.001 mV, post 0.009 ± 0.001 mV.

Left BB Ipsilateral Silent Period

iSPs occurred in 6 of 12 participants. There were no main effects or interactions for iSP\textsubscript{AREA} (all $P > 0.34$). There was no difference in left BB iSP\textsubscript{AREA} between c-tDCS and sham tDCS at baseline ($P > 0.9$). Average iSP\textsubscript{AREA} values were: c-tDCS, pre 0.101 ± 0.022 mV·ms, post 0.106 ± 0.029 mV·ms and sham tDCS, pre 0.099 ± 0.038 mV·ms, post 0.074± 0.035 mV·ms. There were no main effects or interactions for left BB pre-stimulus rmsEMG from these trials (all $P > 0.41$). Average rmsEMG values were: c-tDCS, pre 0.020 ± 0.004 mV, post 0.021 ± 0.005 mV and sham tDCS, pre 0.021 ± 0.004 mV, post 0.022± 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 (Nicolas et al., 2001; Stinear & Byblow, 2004b; Iglesias et al., 2007; Roberts et al., 2008). 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, either 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 propriospinal neurons by c-tDCS

Cathodal 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 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. Non-conditioned MEPs in left BB did not increase after c-tDCS, as would be expected if right M1 was facilitated via interhemispheric projections (c.f., 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. 2008; Chen et al. 2003; 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 after-effects 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 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 (Figure 3c) i.e., there was no evidence that the FAC and SUP components were shifted post c-tDCS. Even given the inter-individual 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; Muellbacher et al., 2000; Davare et al., 2007; Duque et al., 2008; Perez & Cohen, 200). 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 (Tanji et al., 1988; He et al., 1993).

Secondary motor areas in the cat and non-human primate give rise to corticoreticular projections (Andrews et al., 1973; Catsman-Berrevoets & Kuypers, 1976) that modulate excitability of inhibitory interneurons and PNs via the reticulospinal tract (Illert et al., 1978; Illert et al., 1981; Alstermark et al., 1984b, 1984c). Our working hypothesis is that c-tDCS reduced excitation of presumed PNs and inhibitory interneurons via a reduction in excitability of the ipsilateral cortico-reticulospinal descending pathway. Figure 5 illustrates schematically a simplified hypothetical circuit to explain this finding. The presumed C3-4 PNs receive descending inputs from the contralateral corticospinal tract, forming a disynaptic projection to spinal αMNs (Gracies et al., 1994; Mazevet & Pierrot-Deseilligny, 1994; Mazevet et al., 1996; Nicolas et al., 2001). In the cat and non-human primate, higher threshold cortical projections converge onto inhibitory interneurons, interposed with presumed PNs at C3-4 (Alstermark, Lundberg, & Sasaki, 1984a, 1984b, 1984c; Isa, Ohki, Seki, & Alstermark, 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., 1981; Illert et al., 1978). 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 & Byblow, 2004a). This pattern of ipsilateral up-regulation may reflect compensation within the contralesional hemisphere for damage to the ipsilesional corticospinal tract (Ward et al., 2003; Lotze et al., 2006; Ward et al., 2006; Ward et al., 2007; Bestmann et al., 2010). 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, 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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Figure 1. Schematic of the experimental configuration. Left. Probing PN facilitation. The presumed PNs projecting to BB αMNs are subject to excitation by low intensity TMS via descending corticospinal neurons from contralateral M1 (light green lines projecting to PN) and ascending input from ipsilateral median nerve stimulation (red lines projecting to PN). Right. Probing PN inhibition. Stronger TMS intensities recruit higher threshold descending inputs (dark green line) which summate with afferent inputs at the level of the inhibitory interneurons (INH) causing inhibition of presumed PNs. Cx = cortex, CST = corticospinal tract, INH = inhibitory interneuron, PN = propriospinal premotoneuron, FCR = flexor carpi radialis, BB αMNs = biceps brachii alpha motoneurons, TMS = transcranial magnetic stimulation, MNS = median nerve stimulation.

Figure 2. Averaged rectified left BB MEPs from one representative subject showing non-conditioned 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 MEP\textsubscript{AREA} was calculated within the time window depicted between the dashed vertical lines. The ratio of the conditioned to non-conditioned MEP\textsubscript{AREA} (C/NC) is shown at the right (FAC > 1, SUP < 1).

Figure 3. Left BB MEP ratios before (Pre, black bars) and after (Post, grey bars) c-tDCS or sham tDCS. Each bar is the group average (n = 18). There were main effects of COMPONENT, and COMPONENT x TIME and STIMULATION x COMPONENT x TIME interactions. A. Before c-tDCS,
conditioned MEPs were facilitated by median nerve stimulation at TMS intensities near AMT († $P < 0.001$). c-tDCS attenuated the facilitation († $P < 0.001$). There was a difference in FAC after stimulation between conditions (* $P < 0.05$). B. Before c-tDCS, conditioned MEPs were suppressed by median nerve stimulation at higher TMS intensities (** $P < 0.01$). c-tDCS attenuated the suppression († $P < 0.001$). There was a difference in SUP after stimulation between conditions (* $P < 0.05$). 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 = grey bars) c-tDCS to left M1 at four intensities relative to the intensity evoking left BB MEP facilitation. Each bar is the group average (n = 18). Note: F + 2% is the intensity for evoking left BB MEP inhibition. There was no effect of c-tDCS at TMS intensities below F, indicating right M1 motor threshold was unchanged. Error bars indicate SEM.

Figure 4. Right FDI MEP amplitude after c-tDCS and sham tDCS. Each bar represents the group average (n = 18). FDI MEP amplitude was reduced by c-tDCS in comparison to baseline and sham tDCS (* $P < 0.05$). Error bars indicate SEM.

Figure 5. A simplified schematic of proposed after-effects of left M1 c-tDCS. Left. Contralateral and ipsilateral descending inputs to presumed PNs and αMNs. Direct and indirect descending projections from contralateral and ipsilateral CST maintain the balance of excitation and inhibition over presumed PNs for task dependent selective muscle activation. Right. After c-tDCS, ipsilateral descending projections to presumed PNs from the stimulated hemisphere are suppressed (dashed lines). A reduction in excitability of ipsilateral descending projections to
presumed PNs and inhibitory interneurons may reduce task specific selective muscle activation.

RST = reticulospinal tract. All other abbreviations as in Figure 1.

Table 1. The experimental protocol.

Table 2. Non-conditioned left BB MEPAREA at TMS intensities evoking MEP facilitation and inhibition, before and after c-tDCS and sham tDCS. There were no significant findings (all $P > 0.33$).
<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 0</td>
<td>Conditioned &amp; non-conditioned left BB MEPs</td>
</tr>
<tr>
<td>Pre 32</td>
<td>Left BB ISPs</td>
</tr>
<tr>
<td>Pre 32</td>
<td>Right FDI MEPs</td>
</tr>
<tr>
<td></td>
<td>Left M1 r-tDCS or sham r-tDCS 15 min, 1 mA (randomised order)</td>
</tr>
<tr>
<td>Post 0</td>
<td>Rest</td>
</tr>
<tr>
<td>Post 1</td>
<td>Conditioned &amp; non-conditioned left BB MEPs</td>
</tr>
<tr>
<td>Post 12</td>
<td>Left BB ISPs</td>
</tr>
<tr>
<td>Post 12</td>
<td>Right FDI MEPs</td>
</tr>
<tr>
<td>Facilitation component</td>
<td>Inhibition component</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>c-DCS</td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Left EP</td>
<td></td>
</tr>
<tr>
<td>nV/mEP</td>
<td>0.16</td>
</tr>
</tbody>
</table>