A dissociation between propriospinal facilitation and inhibition after bilateral transcranial direct current stimulation

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McCcambridge AB, Stinear JW, Byblow WD. A dissociation between propriospinal facilitation and inhibition after bilateral transcranial direct current stimulation. J Neurophysiol 111: 2187–2195, 2014. First published March 12, 2014; doi:10.1152/jn.00879.2013.—Propriospinal premotoneurons (PNs) are essential for accurate control of the upper limb. They receive bilateral input from premotor (PM) and primary motor (M1) cortices. In humans, excitability of PNs can be estimated from motor-evoked potentials (MEPs) by pairing a descending volley using transcranial magnetic stimulation (TMS) to summate with an ascending volley from peripheral nerve stimulation at the C3–C4 level of the spinal cord. Transcranial direct current stimulation (tDCS) alters excitability of cortical and subcortical areas. A recent study demonstrated that cathodal tDCS can suppress facilitatory (FAC) and inhibitory (INH) components of PN excitability, presumably via effects on corticoreticulospinal neurons (Bradnam LV, Stinear CM, Lewis GN, Byblow WD. J Neurophysiol 103: 2382–2389, 2010). The present study investigated the effects of bilateral tDCS with healthy subjects. The cathode was placed over left dorsal PM or M1 and the anode over right M1 in separate sessions (PM-M1, M1-M1, or Sham). TMS of right M1 elicited MEPs in left biceps brachii across a range of TMS intensities chosen to examine PN-mediated FAC and INH. Conditioning was applied using median nerve stimulation with an interstimulus interval that coincided with TMS and peripheral volleys summatting at the C3–C4 level. All nerve stimulation with an interstimulus interval that coincided with biceps brachii across a range of TMS intensities chosen to examine FAC and INH at slightly higher intensities. By using a reversible blockade, Kinoshita et al. (2012) temporarily blocked synaptic transmission of C3–C4 PNs while sparing other motoneuron inputs. This impaired the monkeys’ ability to reach and grasp accurately. By using a reversible blockade, Kinoshita et al. (2012) confirm C3–C4 PNs are critical in an intact nervous system for producing accurate upper limb movement.

Animal C3–C4 PNs receive input from contralateral and ipsilateral primary motor (M1) and premotor (PM) areas (Andrews et al. 1973; Catsman-Berrevoets and Kuypers 1976). Contralateral input from the crossed corticospinal tract and ipsilateral input from the reticulospinal tract (RST) converge onto α-motoneurons (α-MNs), PNs, and spinhal inhibitory interneurons (INs) rostral to α-MNs in the spinal cord (Boudrias et al. 2010; Brinkman and Kuypers 1973; Catsman-Berrevoets and Kuypers 1976; Illert et al. 1977, 1981). In human and nonhuman primates, descending inputs to spinal INs tonically inhibit C3–C4 PNs (Alstermark et al. 1999; Nicolas et al. 2001; Pierrot-Deseiligny and Burke 2005). This inhibition is released to produce goal-directed movements that require coordination of proximal and distal muscles (Alstermark et al. 2007; Giboin et al. 2012; Isa et al. 2006; Pierrot-Deseiligny 1996; Pierrot-Deseiligny and Burke 2005). Divergent projections of a single PN onto proximal and distal α-MNs have been found in the cat (Alstermark et al. 1990). Such divergence in humans is presumed to assist multijoint coordination of the upper limb (Pierrot-Deseiligny 1996; Pierrot-Deseiligny and Burke 2005).

The C3–C4 propriospinal system can be investigated in humans by pairing peripheral nerve stimulation with transcranial magnetic stimulation (TMS) at an interstimulus interval (ISI) that allows summation of afferent and efferent volleys at C3–C4 PNs (Fig. 1; Bradnam et al. 2011; Nicolas et al. 2001; Stinear and Byblow 2004a,b). This technique can be used to evoke facilitation (FAC) and inhibition (INH) components of presumed propriospinal function. Peripheral nerve stimulation facilitates TMS-induced motor-evoked potentials (MEPs) when combined with low-intensity TMS. Facilitation of the MEP occurs as both volleys summate onto PNs (Bradnam et al. 2011; Nicolas et al. 2001; Robert and Byblow 2004a). A stronger TMS intensity presumably stimulates high-threshold neurons that preferentially innervate INs rostral to PNs (Bradmam et al. 2011; Iglesias et al. 2007; Nicolas et al. 2001; Roberts et al. 2008). Using this technique, the components of propriospinal excitability have been shown to be disinhibited after a stroke (Stinear and Byblow 2004a) and suppressed by ipsilateral M1 cathodal transcranial direct current stimulation (c-tDCS) in healthy participants (Bradnam et al. 2011).

tDCS is a noninvasive brain stimulation technique that can modulate cortical (Lang et al. 2011) and subcortical excitability (Bolzoni et al. 2013b; Lang et al. 2005) by inducing a weak direct current to the brain via electrodes placed over the scalp. The conventional unilateral montage positions an “active”
Neuromodulation of C₃–C₄ propriospinal excitability may be important after stroke for redressing abnormal propriospinal excitability in the affected arm (Mazevet et al. 2003; Stinear and Byblow 2004a). Recently, unilateral tDCS was shown to modulate excitability of descending pathways controlling the ipsilateral proximal upper limb (Bradnam et al. 2011, 2012; McCambridge et al. 2011; O’Shea et al. 2014). Bradnam et al. (2011) found that unilateral M1 c-tDCS suppressed both FAC and INH components of propriospinal excitability to the ipsilateral arm of healthy participants. The present study aimed to investigate the effect of bilateral tDCS on crossed and uncrossed descending pathways affecting PN excitability in healthy participants. Since C₃–C₄ PNs are bilaterally innervated from both PM and M1 (Nathan et al. 1996; Yeo et al. 2012), we investigated placement of the cathode over ipsilateral PM or M1 in separate sessions (M1-M1, PM-M1, and Sham). We expected that FAC and INH would again be suppressed for the arm ipsilateral to the cathode, as previously shown (Bradnam et al. 2011, 2012; McCambridge et al. 2011). However, with bilateral tDCS, we expected that the anode over the contralateral M1 might counteract suppressive effects of the cathodal stimulation on spinal INs, thereby minimizing the effects on PN-mediated INH. We also expected suppression of ipsilateral MEPs (iMEPs) after real tDCS indicative of tDCS effects on uncrossed descending pathways (Bradnam et al. 2011). Given the complexity of the protocol to obtain propriospinal and ipsilateral-mediated MEPs, measures of interhemispheric inhibition could not also be made within the time frame of expected post-tDCS effects and were not studied. Neurophysiological (O’Shea et al. 2014; Sehm et al. 2013), behavioral (Kang and Paik 2011; Mahmoudi et al. 2011; Vines et al. 2008), and computer modelling (Datta et al. 2011; Miranda et al. 2006) studies have highlighted the differential effects of unilateral vs. bilateral tDCS. Understanding bilateral tDCS effects on PN excitability may be an important step toward exploring future clinical applications for tDCS.

METHODS

Participants. Based on sample-size calculations determined from Bradnam et al. (2011) (alpha error probability = 0.05, power = 0.95), 12 healthy adults (mean age = 28.3 yr, range = 21–48 yr, 5 males) without history of upper limb injury or neurological disorder participated in the study. Eleven participants were right-handed, and one participant was ambidextrous, as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). All participants were screened for contraindications to TMS by a neurologist and provided informed, written consent in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee.

Task positions. To examine PN excitability, participants were seated with their left elbow resting on the chair arm rest while holding a 450-g weight in their left hand. The left forearm was supinated, wrist neutral, and fingers loosely gripped the weight. The left hand was held above a surface to maintain a consistent elbow angle of ~90° flexion (45° from horizontal). The right arm remained at rest. This task and posture has been successfully used by others (Bradnam et al. 2011) to facilitate summation of peripheral nerve stimulation and TMS at C₃–C₄ PNs. To evoke iMEPs, both elbows were fixed at 90° flexion, forearms supinated, and wrists strapped to provide resistance. Figure 2, B–D, provides a schematic of the task and subject posture.

Electromyography. Surface electromyography (EMG) was recorded from left and right biceps brachii (BB), left flexor carpi radialis (FCR), and right first dorsal interosseous (FDI) muscles via disposable electrodes (30 × 20 mm; Ambu, Ballerup, Denmark). EMG was...
In right M1, active motor threshold (AMT) was defined for left BB as the minimum stimulus intensity that elicited a 200-μV MEP in four out of eight trials while maintaining task position. Six stimulus intensities were used in this task starting from AMT minus 2% targeting either left PM or premotor (PM; −). PM was defined as 2.5 cm anterior and 1 cm medial to the right first dorsal interosseous (FDI) hot spot. M1 was defined as the BB hot spot. B: task position used to examine facilitatory (FAC) and inhibitory (INH) components of propriospinal excitability. Left BB (LBB) motor-evoked potentials (MEPs) were conditioned with median nerve stimulation (C) in a random order. Rest breaks were taken between blocks to prevent fatigue.

To evoke iMEPs in the left BB, participants performed an isometric bilateral elbow flexion contraction of approximately 30–40% of their maximum. Twelve 100% MSO stimuli were delivered at a rate of 0.2 Hz over the left M1 with rest periods provided to avoid fatigue. Ear plugs were worn by the participants for protection with high stimulation intensities.

cMEPs were also obtained from right FDI at rest pre- (Post0), and 30 min post-tDCS (Post30). The TMS intensity was set to produce stable 1- to 1.5-mV MEPs at baseline.

Median nerve stimulation. A Digitimer DST7A constant current stimulator (Digitimer, Hertfordshire, United Kingdom) delivered 1-ms square-wave pulse to the median nerve of the left arm. The custom-made stimulating clamp comprised a metal ball (9.5-mm diameter) as the cathode and a flat-square (7.3 cm²) metal surface as the anode. The clamp was placed slightly proximal to the medial and lateral epicondyle of the humerus. The cathode was on the medial aspect, and the anode on the lateral aspect of the elbow. The median nerve motor threshold was defined as the minimum current intensity to induce a response (M-wave) of 0.1 mV in FCR while maintaining task position. The median nerve stimulation intensity was set at 0.8× motor threshold to stimulate group I sensory afferents preferentially (Nicolas et al. 2001).

For conditioned trials, median nerve stimulation preceded the TMS pulse to allow summation of the two stimuli at the level of C₅-C₆ PNs. This ISI was based on an estimated 6- ms efferent conduction time from M1 to C₅-C₆ α-MNs and 10-ms afferent conduction time from median nerve stimulation to C₅-C₆ α-MNs. Therefore, a 4-ms ISI would produce summation at the C₅-C₆ BB α-MNs with an additional 3–4 ms expected to produce summation at the C₅-C₆ PNs [see Pierrot-Deseilligny and Burke (2005) for estimation of central conduction times]. The optimal ISI was presumed to be 7–8 ms and optimized for each individual by also considering 6 and 9 ms if necessary (Bradnam et al. 2011). TMS intensity of AMT + 2% MSO was used to collect a randomized block of 12 NC MEPs and 12 C MEPs at ISIs of 7 and 8 ms. The appropriate ISI was chosen when the ratio between the C MEP average and the NC MEP average was >1.1 (ratio = C/NC). A ratio >1 represents facilitation, and <1 inhibition of the MEP. If facilitation was not present at 7 or 8 ms, then a randomized block of 12 NC MEPs and 12 C MEPs at ISIs of 6 and 9 ms was also collected. The ISI that provided the maximum facilitation was chosen as the optimal ISI and remained constant for the experiment.

Study design. Participants completed three experimental sessions of bilateral tDCS. The cathode was placed over left PM or M1, and anode over right M1. tDCS was either real (1 mA, 15 min) or Sham. The sessions were randomized and separated by at least 5 days. Both participants and the experimenter were blinded to stimulation type. tDCS. Bilateral tDCS was delivered with a constant current of 1 mA for 15 min using a Phoresor II stimulator (model PM850; IOMED) via conductive rubber electrodes placed in saline-soaked sponges. The cathode (18 cm²) was placed over the left hemisphere, targeting either left PM or left M1 BB hot spot. The anode (43 cm²) was placed over the right M1 BB hot spot. Left PM was presumed to be located 2.5 cm anterior and 1 cm medial to the FDI electrode montage. EMG signals were acquired using a 750 μV-10 mV gain amplifier (CED 1902; Cambridge Electronic Design, Cambridge, United Kingdom), band-pass filtered (2–1000 Hz), and sampled at 2 kHz (CED 1401).

TMS. Single-pulse TMS was delivered to left and right M1 with a figure-of-eight D70° coil and MagStim 200 unit (MagStim, Dyfed, United Kingdom). The coil was held tangentially to the scalp and positioned to induce current posterior to anterior across the central sulcus. The optimal site for eliciting contralateral MEPs (cMEPs) in the left BB was marked on the scalp over the right hemisphere. The optimal site for eliciting MEPs in the right BB was marked on the scalp over the left hemisphere and used as the “hot spot” for left BB iMEPs. The optimal site for eliciting MEPs in the right FDI was similarly marked over the scalp over the left hemisphere and used to collect MEPs in the right FDI.

Fig. 2. Schematic diagram of the transcranial direct current stimulation (tDCS) electrode positions (A) and participant task positions (B–D). A: the anode was positioned over right M1 (+) and cathode over left M1 or premotor (PM; −). PM was defined as 2.5 cm anterior and 1 cm medial to the right first dorsal interosseous (FDI) hot spot. M1 was defined as the BB hot spot. B: task position used to examine facilitatory (FAC) and inhibitory (INH) components of propriospinal excitability. Left BB (LBB) motor-evoked potentials (MEPs) were conditioned with median nerve stimulation at the elbow during weak elbow flexion. RBB, right BB. C: LBB ipsilateral MEPs (iMEPs) were evoked from left M1 while the participant maintained bilateral isometric elbow flexion. D: right FDI MEPs were collected while the participant was at rest.
ramped up to 1 mA over 15 s and then ramped down from 1 to 0 mA over 30 s (Gandiga et al. 2006) with the placement of the cathode between PM or M1 randomized among participants. Participants were instructed to sit quietly throughout tDCS with their eyes open.

**RESULTS**

**Dependent measures.** Left BB cMEP area was calculated as the integral of the rectified EMG within a 20-ms window from cMEP onset, after subtracting baseline area from an equivalent pretrigger time window, and expressed as a ratio (C/NC) for each TMS intensity. The TMS intensity that produced maximum FAC was AMT or AMT + 2% MSO (median = AMT + 2% MSO). The intensity that produced maximum INH at a TMS intensity higher than FAC was AMT + 4% or AMT + 6% MSO (median = AMT + 6% MSO; see Fig. 3 for example of 1 representative subject). The change in FAC and INH components after tDCS (ΔFAC and ΔINH) was calculated as Δ = post-tDCS − pre-tDCS.

Left BB iMEPs were identified from rectified EMG traces. An iMEP was deemed present when the EMG exceeded the mean pre-trigger EMG + 1 SD for >5 ms within a predetermined iMEP window (18–30 ms; Ziemann et al. 1999). The latency of left BB iMEP was measured from the individual rectified EMG traces. For each participant, the earliest onset and latest offset of the iMEP across all sessions and time points was used as their individualized iMEP window. iMEP area was calculated as the integral of the rectified EMG within each individual’s iMEP window after subtracting an equivalent window of pretrigger EMG. ΔiMEP was calculated as post-tDCS − pre-tDCS.

As a manipulation check for the expected response to tDCS, cMEPs were elicited in right FDI with peak-to-peak amplitude measured and averaged for each time point (pre, post 1, and post 2). ΔcMEP was calculated as post-tDCS − pre-tDCS.

**Statistical analyses.** FAC and INH ratios at baseline were analyzed with one-sample t-tests to confirm a difference from 1 in all sessions. A 2 × component (FAC and INH), 3 × session (M1, PM, and Sham), 2 × time (Pre and Post) repeated-measures ANOVA (rmANOVA) was used to examine for effects of tDCS. ΔFAC and ΔINH were analyzed with paired-sample t-tests to compare each active tDCS session with Sham and one-sample t-tests to test for differences from 0. To assess for other factors that may influence the ratios between sessions, a one-way ANOVA was performed on AMT (%MSO). Two related-sample binomial sign tests compared the stimulation intensity that elicited the FAC or INH component pre- vs. post-tDCS within each session. For each component (FAC and INH), a 3 session (M1, PM, and Sham) × 2 time (Pre and Post) rmANOVA was also performed on the NC MEP area.

Because of unequal prevalence of iMEPs between sessions, paired-sample t-tests were used to compare iMEP latency and area pre- and post-tDCS, and ΔiMEP was analyzed using a one-sample t-test.

A 3-session (M1, PM, and Sham) × 3-time (Pre, Post0, and Post30) rmANOVA was used to investigate changes in right FDI MEP amplitude, and ΔMEP was analyzed using a one-sample t-test.

For all tasks, root-mean-square EMG (EMGrms) was calculated for a 90-ms window before stimulus onset to estimate any effect of contraction strength on MEP data. The left BB EMGrms from the proprioceptive task was assessed with a 3 × session (M1, PM, and Sham), 2 × condition (NC and C), 2 × time (Pre and Post), 6 × intensity (−2%, AMT, +2%, +4%, +6%, and +8%) rmANOVA. The left BB EMGrms from the iMEP task was analyzed using a 3 × 3-time (Pre, Post0, and Post30) rmANOVA. Right FDI EMGrms was analyzed using a 3 × session (M1, PM, and Sham), 3 × time (Pre, Post0, and Post30) rmANOVA.

Effects were deemed significant if P < 0.05. Means ± SE are reported in the text.

**RESULTS**

**Facilitation and inhibition of left BB MEPs.** Before tDCS, FAC and INH were confirmed and differed from 1 in all sessions (all P < 0.002; Fig. 4A). The rmANOVA revealed a main effect of component (F1,11 = 147.15, P < 0.001) with FAC > INH and no other effects. Analysis of the FAC and INH components separately revealed no main effects or inter-
actions (facilitation: session × time interaction, $F_{2,22} = 2.771$, $P = 0.085$; inhibition: session × time interaction, $F_{2,22} = 0.032$ $P = 0.969$). Paired $t$-tests of ΔFAC showed that M1-M1 stimulation $−0.32 ± 0.16$ produced less facilitation than Sham $0.15 ± 0.17$ ($t_{11} = −2.34$, $P = 0.039$), but PM-M1 stimulation $0.05 ± 0.13$ did not differ from Sham ($t_{11} = 0.44$, $P = 0.67$) or M1-M1 stimulation ($t_{11} = 1.84$, $P = 0.094$; Fig. 4B). One-sample $t$-tests confirmed that ΔFAC was significantly reduced relative to baseline after M1-M1 tDCS ($t_{11} = −2.537$, $P = 0.028$) with no other tDCS effects on ΔFAC or ΔINH in any session ($all P > 0.5$). There were no effects of tDCS on ΔINH (M1-M1 $0.017 ± 0.035$, PM-M1 $0.032 ± 0.047$, Sham $0.022 ± 0.045$; all $P > 0.79$).

AMT did not differ between sessions (M1-M1 35% MSO $± 1.6$, PM-M1 34.7% MSO $± 1.3$, Sham 35% MSO $± 1.6$; $F_{2,33} = 0.028$, $P = 0.972$). The TMS intensity that elicited FAC (AMT + 1.4% MSO $± 0.24$) and INH (AMT + 5.47% MSO $± 0.22$) was not changed by tDCS ($all P > 0.109$). The NC MEP area was not changed by tDCS in either session for either FAC or INH components ($all P > 0.084$).

Left BB iMEPs. iMEPs were present in all 3 sessions for 7/12 participants and in 2 sessions only for 3/12 participants. iMEP area showed no significant differences pre- to post-tDCS ($all P > 0.54$). ΔiMEP was not significantly different from 0 ($all P > 0.54$). iMEP latency was unchanged pre- to post-tDCS ($all P > 0.15$; M1, pre = 19.04 ± 0.77 ms, post = 20.06 ± 0.58 ms; PM, pre = 19.77 ± 0.29 ms, post = 19.8 ± 0.60 ms; Sham, pre = 20.99 ± 0.56 ms, post = 20.35 ± 0.65 ms).

Right FDI. There were no main effects or interactions for FDI MEP amplitude ($all P > 0.18$). One-sample $t$-tests of post 1 and post 2 changes revealed no significant differences from baseline ($all P > 0.125$).

Pretrigger EMG. For all muscles and tasks analyzed, there were no main effects or interactions for pretrigger EMG (M1 iMEP, pre = 0.18 ± 0.03 mV vs. post = 0.24 ± 0.05 mV, $P = 0.079$; all others, $all P > 0.195$).

**DISCUSSION**

In the present study, median nerve-conditioned TMS was used to examine the effects of tDCS on spinally mediated excitability in the upper limb. We found several confirmatory and novel results. First, median nerve conditioning facilitated left BB MEPs when combined with a low TMS intensity and inhibited left BB MEPs with a slightly higher TMS intensity. This was consistent with previous studies examining propriospinal modulation of upper limb α-MNs (Bradnam et al. 2011; Nicolas et al. 2001; Stinear and Byblow 2004a,b). Second, tDCS had effects on spinal networks controlling the upper limb ipsilateral to the cathode (Bradnam et al. 2011; McCambridge et al. 2011). The primary novel finding was that M1-M1 tDCS compared with Sham suppressed PN-mediated FAC without affecting INH to the ipsilateral upper limb (BB). To our knowledge, this is the first indication that tDCS may differentially modulate FAC and INH. Surprisingly, there were no effects of PM-M1 tDCS on propriospinal excitability. Potential mechanisms underlying these findings are discussed.

Previously, M1 c-tDCS was shown to suppress both FAC and INH components acting on ipsilateral BB α-MNs (Bradnam et al. 2011). Here, we found that M1-M1 tDCS had suppressive effects over the FAC component only. Both studies positioned the cathode over ipsilateral left M1 and used current amplitude of 1 mA for 15 min. Changes in corticomotor excitability after M1 tDCS have been proposed to occur via polarity-dependent shifts in the resting membrane potential, whereby stimulation from the anode facilitates and cathode inhibits left BB MEPs with a slightly higher TMS intensity. This was consistent with previous studies examining proprioceptive input to PNs and INs in the ipsilateral BB. Therefore, the differential modulation of PN components in the present bilateral montage study compared with the previous unilateral montage study seems likely to be, at least in part, due to the anode over contralateral right M1 during bilateral M1-M1 tDCS. However, the site of action of anodal stimulation within the bilateral montage is unlikely to be cortical in origin. If right M1 had been facilitated after cathodal-anodal M1-M1 tDCS, we would expect left BB NC MEP area to increase and/or the TMS intensity that elicited FAC or INH to decrease. This was not observed in the present study or previously after unilateral left M1 c-tDCS (Bradnam et al. 2011). Given that M1-M1

![Graph A](image1.png)

![Graph B](image2.png)

**Fig. 4.** Group averages ($n = 12$) of LBB MEP facilitation (black) and inhibition (gray) across all sessions (M1-M1, Sham, and PM-M1). A: pre-tDCS ratios are shown. Both facilitation and inhibition were different from 1 (horizontal dashed line; **$P < 0.002$). B: change in FAC and INH components after tDCS ($Δ$) ratios are shown. Facilitation was suppressed after M1-M1 tDCS, and Δfacilitation was different between M1-M1 and Sham sessions (**$P < 0.05$). Error bars indicate SE.
tDCS did not change NC MEP area, we propose the effects of tDCS on propriospinal excitability may be, at least in part, occurring at a subcortical level. That perhaps involves modulation of bulbospinal descending projections that are known to have dense connections with PNs in the cat (Alstermark et al. 1984b; Illert et al. 1978, 1981). Our data support a growing body of evidence that tDCS is capable of influencing excitability of subcortical and spinal structures (Bolzoni et al. 2013a,b; Bradnam et al. 2013; Roche et al. 2009, 2012).

Neuroimaging, animal, and computer modelling studies have illustrated the vast effects of tDCS throughout the brain (Bolzoni et al. 2013b; Datta et al. 2012; Lindenberg et al. 2013; Sehm et al. 2013), including effects on subcortical structures such as the RST, as observed directly in the cat after anodal stimulation (Bolzoni et al. 2013b), and the midbrain and brain stem during bilateral tDCS in humans (Sehm et al. 2013). Functional connectivity measured during and after tDCS using resting-state functional magnetic resonance imaging demonstrates the effects of tDCS are network-wide and dynamic over time (Sehm et al. 2013). The differential effects of bilateral and unilateral tDCS may relate to the direction of current passed through the brain. Bilateral tDCS induces current directed medial to lateral in the brain, whereas unilateral tDCS induces current dorsal to ventral. In hippocampal slice preparations, the current direction relative to axonal or dendritic orientation is important for determining the direction and degree of neural excitability changes (Kabakov et al. 2012). The direction of current through the whole brain may preferentially modulate different motor areas or disproportionately modulate the same areas. It is possible that cortical and subcortical neural populations interconnected with the cervical propriospinal system may be modulated differentially between unilateral and bilateral tDCS, leading to separate modulation of the INH component between studies. Modelling the effects of tDCS throughout the central nervous system is an important step that may begin to elucidate these matters.

Current explanations of tDCS on human propriospinal excitability are necessarily indirect and somewhat speculative. We propose that bilateral tDCS suppressed PN-mediated FAC via similar mechanisms as those proposed by Bradnam et al. (2011) after unilateral c-tDCS, whereby cathodal stimulation of ipsilateral M1 reduced excitability of ipsilateral corticoreticulospinal inputs to PNs and INs. The novel finding was the preservation of INH after M1-M1 tDCS compared with unilateral c-tDCS. This may relate to placement of the anode over contralateral M1 within the bilateral montage. As depicted in Fig. 1, PNs and INs are innervated by ipsilateral and contralateral M1 (Andrews et al. 1973; Catsman-Berrevoets and Kuypers 1976). Anodal stimulation of contralateral M1 may have facilitated descending contralateral inputs to INs and PNs, thereby counterbalancing suppression from the cathode. Given that afferent input is stronger to INs relative to PNs, so may be the efferent input, thus permitting a stronger effect of anodal stimulation on inhibitory INs compared with PNs (Fig. 1, thicker input to IN; Alstermark et al. 1984a; Pierrot-Deselligny and Burke 2005). This explanation is almost certainly too simplistic but is intended as a starting point for future hypothesis generation. The effects of bilateral tDCS may be more complicated than simply up- and downregulating descending pathways from M1 and may also involve bihemispheric interactions that were not measured (Lindenberg et al. 2013). M1-M1 tDCS may have increased interhemispheric inhibition from right M1 to left M1, thereby suppressing the ipsilateral cortico-reticulo-propriospinal pathway leading to the observed suppression of PN-mediated FAC. How tDCS modulates excitability at the level of the spinal cord is a topic of ongoing investigation and requires further systematic evaluation of parameters such as electrode montage, current density, and intersession interval, for example, all of which will be important for optimizing tDCS.

PM-M1 tDCS did not alter propriospinal excitability. To our knowledge, this is the first study to examine PM-M1 bilateral tDCS. Stimulation of PM using unilateral tDCS montages has been investigated in three studies with mixed results (Boros et al. 2008; Kirimoto et al. 2009, 2011). Kirimoto et al. (2009, 2011) found PM anodal and cathodal stimulation suppressed and facilitated cMEPs, respectively, but only with an electrode ≥18 cm², whereas Boros et al. (2008) found no change after PM anodal or cathodal tDCS on MEP amplitude with single-pulse TMS. The effects of direct current stimulation targeting PM appear less robust than M1 stimulation. This may account for the lack of PM-M1 tDCS effects in the present study. In addition, we cannot rule out the possibility that cathodal-anodal PM-M1 tDCS could have had a cancelling or ceiling effect on C3–C4 propriospinal excitability. Future research should consider the use of neuronavigation to ensure placement of electrodes is accurate for tDCS of nonprimary motor areas.

There are a number of limitations to the present study. Based on previous studies, scalp measurements were used to determine placement of the cathode over PM. This method is unlikely to account for anatomic interindividual differences. Error in the placement of the electrode over PM may have increased the variability of the stimulation effect. Right FDI MEPs were collected pre- and post-tDCS as a manipulation check for the expected direction of modulation. Nitsche et al. (2007) found that using a small tDCS electrode targeted to abductor digitii minimi selectively modulated MEP amplitude of this muscle but not the adjacent FDI. It is possible FDI MEP amplitude was not significantly modulated after M1-M1 tDCS because the small 18-cm² cathode was targeted to right BB and not FDI hot spot. A limitation to comparing bilateral tDCS in the present study with unilateral tDCS in the previous study (Bradnam et al. 2011) is the electrode sizes and thus current density were not the same (18 cm², 0.056 mA/cm²; 35 cm², 0.029 mA/cm²). A smaller cathode was used to ensure separation between PM and M1. Previous studies that manipulated current density by altering current amplitude show the extent of modulation and even the direction of change can be affected (Bastani and Jaberzadeh 2013; Batsikadze et al. 2013). To our knowledge, manipulating the size of the cathode while maintaining current amplitude during c-tDCS or M1-M1 tDCS has not yet been examined. However, the possible influence of these differences should not be ignored.

Left BB iMEP area was not significantly different after M1-M1 tDCS, possibly owing to a lack of statistical power. iMEPs were successfully elicited in 7 out of 12 participants in all 3 sessions and 3 participants in 2 sessions. Considering iMEPs are not easily found in healthy participants, this was a moderate success rate compared with other studies (Bradnam et al. 2010; McCambridge et al. 2011; Netz et al. 1997). iMEPs are also highly variable (Ziemann et al. 1999), therefore when combined with a small sample size this makes them difficult to
study. One study found c-tDCS suppressed iMEPs in the infraspinatus during a unilateral but not a bilateral contraction task that was used in this study (Bradnam et al. 2010). The infraspinatus is also more proximal than BB and perhaps receives a greater proportion of ipsilateral input relative to BB. Investigating both crossed and uncrossed descending pathways is important to further our understanding of the effects of tDCS. Modulating excitability of ipsilateral uncrossed descending pathways may be of particular importance after stroke when the contralesional ipsilateral pathway to the paretic arm becomes upregulated (Bradnam et al. 2012, 2013; Schwerin et al. 2008, 2011).

After a stroke, many survivors experience impairment of the upper limb. Stereotypical coupling between shoulder and elbow movement and abnormal cocontraction of upper limb muscles can impair the functional ability of the arm (Brunnstrom 1970; Twitchell 1951). Similar to the present study, peripheral nerve-conditioned TMS has been used to examine the components of propriospinal excitability in chronic stroke patients (Stinear and Byblow 2004a). Compared with healthy controls, FAC was increased and INH was decreased or not present in the paretic arm (Stinear and Byblow 2004a). Because of the divergent projections of PNs, upregulation or disinhibition of C3–C4 PNs make this a candidate neural system underlying abnormal muscle coupling after stroke (Mazevet et al. 2003; Pierrot-Deseilligny and Burke 2005; Stinear and Byblow 2004a). In particular, upregulation of the contralesional ipsilateral cortico-recticulo-propriospinal pathway (depicted in Fig. 1) has been implicated in the expression of flexor or extensor synergies after stroke (Bradnam et al. 2013; Ellis et al. 2012). Selective suppression of FAC while maintaining INH after M1–M1 tDCS could be useful for reducing excitability of PNs. This may offer utility in promoting recovery of upper limb function. In patients with chronic stroke, M1–M1 tDCS has been shown by others to improve hand and arm function (Bologna et al. 2011; Lindenberg et al. 2010, 2012; Mahmoudi et al. 2011). Despite this, it is unlikely that one neuromodulation technique or tDCS montage will suit all patients. Upregulation of propriospinal excitability in the paretic arm may be an adaptive change in some patients (Bradnam et al. 2013; Pierrot-Deseilligny 1996). Therefore, future research to distinguish markers that could identify a suitable tDCS montage for an individual patient would likely improve the efficacy of stimulation.

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AUTHOR CONTRIBUTIONS

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