Cathodal transcranial direct current stimulation of the primary motor cortex improves selective muscle activation in the ipsilateral arm

Alana B. McCambridge, Lynley V. Bradnam, Cathy M. Stinear, and Winston D. Byblow

Movement Neuroscience Laboratory, Department of Medicine, and Centre for Brain Research, The University of Auckland, Auckland, New Zealand

Submitted 28 February 2011; accepted in final form 18 April 2011

Cathodal transcranial direct current stimulation of the primary motor cortex improves selective muscle activation in the ipsilateral arm. J Neurophysiol 105: 2937–2942, 2011. First published April 20, 2011; doi:10.1152/jn.00171.2011.—Proximal upper limb muscles are represented bilaterally in primary motor cortex. Goal-directed upper limb movement requires precise control of proximal and distal agonist and antagonist muscles. Failure to suppress antagonist muscles can lead to abnormal movement patterns, such as those commonly experienced in the proximal upper limb after stroke. We examined whether noninvasive brain stimulation of primary motor cortex could be used to improve selective control of the ipsilateral proximal upper limb. Thirteen healthy participants performed isometric left elbow flexion by contracting biceps brachii (BB; agonist) and left forearm pronation (BB antagonist) before and after 20 min of cathodal transcranial direct current stimulation (c-tDCS) or sham tDCS of left M1. During the tasks, motor evoked potentials (MEPs) in left BB were acquired using single-pulse transcranial magnetic stimulation of right M1 150–270 ms before muscle contraction. As expected, left BB MEPs were facilitated before flexion and suppressed before pronation. After c-tDCS, left BB MEP amplitudes were reduced compared with sham stimulation, before pronation but not flexion, indicating that c-tDCS enhanced selective muscle activation of the ipsilateral BB in a task-specific manner. The potential for c-tDCS to improve BB antagonist control correlated with BB MEP amplitude for pronation relative to flexion, expressed as a selectivity ratio. This is the first demonstration that selective muscle activation in the proximal upper limb can be improved after c-tDCS of ipsilateral M1 and that the benefits of c-tDCS for selective muscle activation may be most effective in cases where activation strategies are already suboptimal. These findings may have relevance for the use of tDCS in rehabilitation after stroke.

Address for reprint requests and other correspondence: W. D. Byblow, Movement Neuroscience Laboratory, Dept. of Sport & Exercise Science, Centre for Brain Research, The Univ. of Auckland, Auckland 1142, New Zealand (e-mail: w.byblow@auckland.ac.nz).
brain. Our reasoning was as follows. TMS produces a number of descending volleys in the corticospinal pathway, probably due to multiple intracortical synaptic connections onto pyramidal neurons. The descending volleys are termed I-waves, with I1 being the first volley 1.5 ms poststimulus, reflecting one synapse onto pyramidal neurons, and I3 normally the last wave 4.5 ms after the stimulus. I1 and I3 waves are thought to represent activation of distinct populations of cortical interneurons (INs) (Sakai et al. 1997). I1 waves are preferentially produced when TMS generates PA current flow in M1, whereas I3 waves are preferentially produced by AP current flow (Hanajima et al. 1998).

In this study, we predicted that c-tDCS of left M1 would improve selective activation of ipsilateral BB. In particular, we hypothesized that c-tDCS would selectively decrease BB MEP amplitude in the ipsilateral limb before pronation but not flexion and that left BB iMEPs would be suppressed after left M1 c-tDCS. To explore possible transcallosal-mediated effects of c-tDCS (Bradnam et al. 2010b), we examined ipsilateral silent periods (iSPs) in left BB. To further elucidate the underlying mechanisms of c-tDCS (Bradnam et al. 2010b), we recorded contralateral first dorsal interosseous (FDI) MEPs and BB iMEPs and iSPs using TMS that induced current flow in the brain both PA and AP (DiLazzaro et al. 2001; Ziemann et al. 1999).

METHODS
Participants. Thirteen healthy adults (mean age 22.7 yr, range 18–41 yr, 5 males) without history of upper limb injury or neurological disorder participated in the study. All participants were right-handed, assessed with the Edinburgh Handedness Inventory (Oldfield 1971). Participants were screened for contraindications to TMS by a neurologist. All participants gave written informed consent, and the local ethics committee approved the study in accordance with the Declaration of Helsinki.

Electromyography. Surface electromyography (EMG) was recorded from the left BB, the left PT, and the right FDI via disposable electrodes (30 × 20 mm; Ambu, Ballerup, Denmark). Standard skin preparation procedures were used. BB and PT electrodes were placed over the muscle bellies in a bipolar montage. The right FDI electrodes were placed in a belly-tendon montage. EMG signals were amplified (Grass P511AC AMG), bandwidth-filtered (3–1,000 Hz), sampled at 2 kHz, and processed using Signal software (CED, Cambridge, United Kingdom).

Design and protocol. Participants completed two experimental sessions, receiving either c-tDCS or sham tDCS, in a randomized double-blind crossover design with sessions separated by at least 5 days. Figure 1A illustrates data collection during the motor task. A flow chart of the experiment is shown in Fig. 1B.

Motor tasks. Participants were seated in a chair with their left arm strapped firmly to a table at an elbow angle of 90° and the wrist in a neutral semisupinated position. The right arm rested on a cushion over their lap. Participants performed three tasks with their left arm. They performed rhythmic isometric pronation or isometric elbow flexion paced by a 1-Hz metronome. EMG signals were amplified (Grass P511AC AMG), bandwidth-filtered (3–1,000 Hz), sampled at 2 kHz, and processed using Signal software (CED, Cambridge, United Kingdom).

To examine left BB iMEPs and iSPs, participants maintained isometric elbow flexion at 50% maximum voluntary contraction (MVC) with their left arm, whereas TMS was applied over left M1. TMS. TMS was delivered with a figure-of-eight coil (70 mm) connected to a Magstim stimulator. The optimal site for eliciting contralateral MEPs in left BB was marked on the scalp over the right hemisphere, and for eliciting MEPs in right FDI over the left hemisphere.
µV during a 50-ms window before stimulus onset. Average BB MEP amplitude was obtained for the both pronation and flexion tasks for the accepted trials. BB MEP amplitude before pronation was expressed as a ratio of the BB MEP amplitude before flexion to obtain a measure of SR (Gerachshenko et al. 2008; Gerachshenko and Stinear 2007).

iMEPs and iSPs were obtained in left BB from 32 stimuli delivered to left M1 at 90% of maximal stimulator output. The coil was positioned over the right BB hot spot and oriented to induce current in a PA or AP direction (16 stimuli each). TMS was delivered at a rate of 0.2 Hz during contraction of BB at 50% MVC with rest breaks after every few stimuli.

During complete rest, right FDI MEPs were collected as a manipulation check for contralateral effects. A stimulation intensity that produced a response of ~50% of the maximum MEP amplitude in the resting FDI was used. The first block was collected with the coil positioned over the FDI hot spot to induce PA current and then AP current (16 stimuli each).

tDCS. c-tDCS was delivered with a constant current of 1 mA for 20 min using a Phoresor II stimulator (Model PM850; IOMED) via conductive rubber electrodes placed in saline-soaked sponges. The cathode was positioned over the right M1 BB hot spot. The anode was positioned above the right orbit, in accordance with established protocols (Nitsche et al. 2007). A 75-cm² electrode was used for the anode, and a 35-cm² electrode was used for the cathode. An unblinded experimenter applied the real or sham stimulation but took no part in data collection or analysis. For sham stimulation, the current was ramped down from 1 to 0 mA within 30 s (Gandiga et al. 2006). Participants sat quietly throughout tDCS and for 5 min afterward as a period of consolidation.

Statistical analysis. Peak-to-peak BB MEP amplitude, SR, pre-stimulus rmsEMG, and prestimulus time to EMG burst onset were analyzed. Left BB MEP amplitude was analyzed with a 2 stimulation (c-tDCS, sham) × 2 time (Pre, Post) rmANOVA for each task (flexion, pronation). SR was analyzed with a 2 stimulation (c-tDCS, sham) × 2 time (Pre, Post) rmANOVA. A linear regression of SR was performed between preintervention values and the change in ratio (ΔSR = Post − Pre). Pretrigger rmsEMG and time to EMG onset were analyzed with a 2 stimulation (c-tDCS, sham) × 2 task (flexion, pronation) × 2 time (Pre, Post) rmANOVA.

Left BB EMG traces were rectified, averaged, and inspected for iMEPs or iSPs. iMEPs were deemed present if values > 2 SD above the mean prestimulus EMG activity occurred 15–45 ms poststimulus (Chen et al. 2003; Lewis and Perreault 2007). For each individual, the earliest onset and latest offset times were used to calculate iMEP area, and this window was used across all time points for the session. Background EMG was calculated in a window of equivalent duration and subtracted from iMEP area as a normalization procedure (Bradnam et al. 2010a). Trials without iMEPs were inspected for iSPs. An iSP was deemed present if the area starting within 20–35 ms after the stimulus was below the mean prestimulus EMG level for >10 ms (Chen et al. 2003; Trompetto et al. 2004). Ipsilateral SP areas from PA and AP stimulation were pooled to increase the number of observations. In participants with iSPs, left BB iSP area was analyzed using a 2 stimulation (c-tDCS, sham) × 2 time (Pre, Post) rmANOVA.

Right FDI MEP amplitude and latency for both PA and AP current directions were analyzed with a 2 stimulation (c-tDCS, sham) × 2 direction (PA, AP) × 2 time (Pre, Post) rmANOVA.

Paired t-tests were used to explore post hoc effects of interactions. Since all factors in the design have only two levels, corrections for multiple comparisons were not deemed necessary. Effects were deemed significant if P < 0.05. Means ± SD are reported in the text.

RESULTS

Figure 2 contains example trace figures from a single participant showing EMG and MEPs from left BB.

Left BB MEP amplitude. Left BB MEP amplitudes before pronation were suppressed after c-tDCS but not sham stimulation. There was a stimulation × time interaction (F1,12 = 4.846, P = 0.048) with no main effects of time (F1,12 = 3.17, P = 0.1) or stimulation (F1,12 = 0.91, P = 0.346). Left BB MEP amplitude before pronation did not differ between stimulation, task, and time for time to EMG onset or pretrigger rmsEMG (all F < 1).

Although SR appeared to decrease after c-tDCS (Pre: 0.295, Post: 0.174), the stimulation × time interaction on BB MEP amplitude before flexion (all F > 1,12 F0.05 = 4.846) with no effect of time (F1,12 = 1.138, P = 0.281).

There was no effect of stimulation, time, or stimulation × time interaction on BB MEP amplitude before flexion (all P > 0.1).

SR. There was a main effect of stimulation (F = 4.95, P = 0.046) with no effect of time (F1,12 = 3.21, P = 0.098). Although SR appeared to decrease after c-tDCS (Pre: 0.295 ± 0.35; Post: 0.174 ± 0.12) but not sham (Pre: 0.292 ± 0.22; Post: 0.296 ± 0.34), the stimulation × time interaction was not significant (F1,12 = 0.228, P = 0.6).

Figure 4 shows the relationship between ΔSR and baseline SR. A linear regression analysis revealed that the ΔSR was negatively correlated with baseline SR after c-tDCS (r² = 0.906, F = 106.44, P < 0.001) but not sham tDCS (r² = 0.129, F = 1.630, P = 0.228). The higher the baseline SR, the more SR decreased after c-tDCS.

EMG. There were no main effects or interactions of stimulation, task, and time for time to EMG onset or pretrigger rmsEMG (all F > 1). The mean EMG burst onset time after stimulation was 28.2 ms for the flexion task and 137.2 ± 33.4 ms for the pronation task.

iMEPs and iSPs. Left BB iMEPs occurred in six participants in the c-tDCS session, five participants in the sham session, and six participants for both AP and PA directions. Paired t-tests
indicated no differences between current directions on iMEP area or iSP area (both \( P < 0.1 \)). iMEP areas from PA and AP stimulation were then pooled to increase the number of observations. Because of unequal observations, these data were not amenable to ANOVA. Paired \( t \)-tests compared pre- and post-iMEP area for c-tDCS and sham sessions separately and indicated no effect of time for either stimulation type (c-tDCS Pre: 1.718 ± 1.13 mV·ms, Post: 1.433 ± 1.13 mV·ms; sham Pre: 1.984 ± 1.62 mV·ms, Post: 2.235 ± 2.46 mV·ms; both \( P > 0.1 \)).

iSPs were determined from traces where an iMEP was not present. Six participants had iSPs from both PA and AP current directions, and four participants showed iSPs from one direction only. There were no main effects or interactions observed for iSP area (all \( P > 0.1 \)).

Right FDI MEP amplitude and latency. For MEP amplitude, there was a main effect of stimulation (\( F_{1,12} = 6.713, P = 0.024 \)) and direction (\( F_{1,12} = 19.870, P = 0.001 \)), with a direction \( \times \) time (\( F_{1,12} = 4.937, P = 0.046 \)) and stimulation \( \times \) time interaction (\( F_{1,12} = 6.809, P = 0.023 \)). FDI MEPs-elicited PA were suppressed after c-tDCS stimulation (\( t_{12} = 2.681, P = 0.02 \)) but not after sham (\( P > 0.1 \)). FDI MEPs-elicited AP did not differ after c-TDCS or sham stimulation (\( P > 0.1 \); Fig. 5).

Right FDI MEP latency was shorter following PA stimulation (24.6 ± 0.4 ms) than AP stimulation (26.6 ± 5.8 ms) (\( F_{1,12} = 49.699, P < 0.001 \)). There was a main effect of time (\( F_{1,12} = 6.915, P = 0.022 \)) and a stimulation \( \times \) orientation interaction (\( F_{1,12} = 5.182, P = 0.042 \)). The effect of time arose because FDI MEP latency increased from 25.2 to 26.0 ms.
seems unlikely. The reference electrode was 75 cm² in the "due to a difference in size of the tDCS electrodes, but this iMEPs/iSPs and their modulation after c-tDCS may have been (Bradnam et al. 2010b). Given that infraspinatus is more proportion was similar to those observed in infraspinatus pants. The lack of iSP and iMEP modulation after c-tDCS is unfortunately, iMEPs were observed in only 6 of 13 partici-
c-tDCS would suppress left BB iMEPs in the current study. This is likely due to a floor effect in participants with a low baseline SR. Healthy participants typically have low SRs and therefore less capacity for improvement (Gerachshenko et al. 2008). Despite the apparent trend for improved SR after c-tDCS, the stimulation × time interaction did not reach conventional levels of significance. Regardless, c-tDCS reliably suppressed BB MEP amplitude before pronation of the ipsilateral arm.

In light of previous results that c-tDCS of M1 can suppress excitability of projections to both the contralateral and ipsilateral infraspinatus (Bradnam et al. 2010b), we hypothesized that c-tDCS would suppress left BB iMEPs in the current study. Unfortunately, iMEPs were observed in only 6 of 13 participants. The lack of iSP and iMEP modulation after c-tDCS is likely to be due to a lack of statistical power. However, this proportion was similar to those observed in infraspinatus (Bradnam et al. 2010b). Given that infraspinatus is more proximal than BB, and therefore under more widespread bilateral control, this may account for the difference in results between the two studies. Another reason for the lack of BB iMEPs/iSPs and their modulation after c-tDCS may have been due to a difference in size of the tDCS electrodes, but this seems unlikely. The reference electrode was 75 cm² in the current study and 35 cm² in the previous study, however, this would not change the current density under the target (M1) electrode, and no such differences in contralateral MEP size had been noted on the basis of reference electrode dimension previously (Nitsche et al. 2007). Because of the small number of observations, it is unclear whether c-tDCS reliably modulated iMEPs and iSPs in our study.

The majority of M1 tDCS studies have found c-tDCS to be effective at suppressing corticomotor excitability to contralateral muscles of the hand when tested with PA stimulation (Nitsche et al. 2007; Nitsche and Paulus 2000). In the present study, c-tDCS suppressed right FDI MEP amplitude obtained with PA TMS, which preferentially activates I1 waves, but not AP TMS, which preferentially activates I3 waves. I1 and I3 waves represent activation of distinct populations of cortical neurons (Sakai et al. 1997). AP stimulation preferentially activates late I3 waves that are most susceptible to intracortical inhibition, measured with short-latency paired-pulse PA TMS (Hanajima et al. 1998). c-tDCS can appear to enhance intracortical inhibition in M1 as evidenced by smaller conditioned MEPs (Nitsche et al. 2005). However, this apparent increase in inhibition is likely due to suppression of I1 waves by c-tDCS, resulting in MEPs that mostly comprise later I3 waves and are therefore more susceptible to intracortical inhibition (Hanajima et al. 2008). The current study provides an indication that c-tDCS may suppress cortical neurons responsible for the early I1 wave (Nitsche et al. 2005). To our knowledge, this is the first to demonstrate that contralateral FDI MEPs from AP TMS were unaffected by c-tDCS.

Potential mechanisms. The pathways mediating the observed effects of c-tDCS on left BB MEPs before pronation cannot be ascertained directly from this study. However, there is reason to suspect that the ipsilateral reticulospinal tract (RST) may be involved. Animal studies indicate that descending excitation from ipsilateral M1 via the RST terminates on feedforward inhibitory INs that maintain tonic inhibitory control over C3–C4 PNs (Alstermark et al. 1984a,b; Isa et al. 2006). PNs have direct facilitatory inputs onto agonist α-motoneurons (αMNs) and INs that synapse onto antagonist αMNs (Alstermark et al. 1990a,b; Tantisira et al. 1996). In healthy humans, we expect that this ipsilateral M1-RST pathway is downregulated for certain tasks. For example, before pronation, downregulation would disinhibit (i.e., facilitate) PNs that suppress antagonist BB αMNs. Conversely, disinhibition of PNs does not facilitate agonists (BB MEP amplitude before flexion), since agonist control is mediated primarily via the contralateral M1 (Connolly and Forssberg 1997; Lemon 2008). Intriguingly, there is indirect evidence that M1 c-tDCS can suppress input to putative PNs controlling ipsilateral BB in healthy humans (Bradnam et al. 2011). In the current study, c-tDCS may have enhanced the downregulation of the ipsilateral M1-RST pathway and hence further suppressed antagonist BB in the pronation task. The enhanced suppressive effect after c-tDCS would be expected to be largest for those with weaker baseline downregulation (highest SR), and indeed this was the case. Although these ideas are speculative, modulation of the putative PN system via the RST after c-tDCS may explain the reduced BB MEP amplitudes observed before pronation in the ipsilateral arm, providing a possible explanation for why c-tDCS effects were task-dependent and specific to antagonist control. A more detailed description and schematic model of c-tDCS effects on the putative PN system are described in Bradnam et al. (2011; see their Fig. 5). Whatever the mechanism, ipsilateral c-tDCS may
be of utility for improving selective muscle activation in cases where the ipsilateral M1 is overexcitable.

Potential clinical implications. The ability to suppress cortico-motor excitability of the antagonist before contraction may have clinical utility for upper limb recovery after stroke. In some patients after stroke, excessive excitability of ipsilateral descending pathways from the contralesional hemisphere can lead to abnormal upper limb synergies, which are characterized by an inability to suppress antagonist muscles (Bradnam et al. 2010; Gerachshenko et al. 2008; Schwerin et al. 2008). The current study provides the first demonstration that c-tDCS of ipsilateral M1 can improve precontraction suppression of the antagonist in the proximal upper limb of healthy participants. It is unlikely that any single neuromodulation technique like c-tDCS will be an effective adjuvant for motor rehabilitation for all stroke patients (Schlau et al. 2008; Stinear 2010). Future studies may usefully identify the characteristics of patients for whom c-tDCS of the contralesional hemisphere may be beneficial.

ACKNOWLEDGMENTS

We thank Fred Noten for assistance during data collection and Jim Stinear for helpful comments.

DISCLOSURES

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

REFERENCES