Cathodal transcranial direct current stimulation (c-tDCS) can reduce excitability of neurons in primary motor cortex (M1) and may facilitate motor recovery after stroke. However, little is known about the neurophysiological effects of tDCS on proximal upper limb function. We hypothesized that suppression of contralesional M1 (cM1) excitability would produce neurophysiological effects that depended on the severity of upper limb impairment. Twelve patients with varying upper limb impairment after subcortical stroke were assessed on clinical scales of upper limb spasticity, impairment, and function. Magnetic resonance imaging was used to determine lesion size and fractional anisotropy (FA) within the posterior limbs of the internal capsules indicative of corticospinal tract integrity. Excitability within paretic M1 biceps brachii representation was determined from motor-evoked potentials during selective isometric tasks, after cM1 sham stimulation and after c-tDCS. These neurophysiological data indicate that c-tDCS improved selective proximal upper limb control for mildly impaired patients and worsened it for moderate to severely impaired patients. The direction of the neurophysiological effects of c-tDCS was strongly related to upper limb spasticity, impairment, function, and FA asymmetry between the posterior limbs of the internal capsule. These results indicate systematic variation of cM1 for proximal upper limb control after stroke and that suppression of cM1 excitability is not a "one size fits all" approach.

Keywords: corticospinal tract, ipsilateral pathways, magnetic resonance imaging, stroke prediction, transcranial direct current stimulation

Introduction

Six months after stroke, up to two-thirds of patients are unable to incorporate a weak hand into activities of daily living (Dobkin 2005). Following stroke there is often an imbalance in primary motor cortex (M1) excitability, with relative under-excitability in the stroke affected ipsilesional hemisphere and relative overexcitability in the contralesional hemisphere, and worse outcomes for patients with greater imbalance (Traversa et al. 1998). Rebalancing of cortical excitability in patients with stroke has been associated with improvement of upper limb function (Traversa et al. 1998; Shimizu et al. 2002; Murase et al. 2004; Stinear et al. 2008; Swayne et al. 2008) and can be promoted with noninvasive brain stimulation (Hummel and Cohen 2006). Transcranial direct current stimulation (tDCS) is a form of noninvasive brain stimulation that suppresses or facilitates M1 depending on the electrode polarity (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003; Nitsche et al. 2005). Cathodal tDCS (c-tDCS) hyperpolarizes neurons and can be used to reduce the relative overexcitability of the contralesional hemisphere (Nowak et al. 2009).

Proximal upper limb muscles are innervated by projections from contralateral and ipsilateral motor cortex, and this bilateral pattern of organization has functional implications for adjuvants such as tDCS (Kuypers and Brinkman 1970; Turton et al. 1996; Lemon 2008). There is recent evidence in healthy adults that suppression of M1 can influence control of the ipsilateral proximal upper limb by reducing or increasing excitability of ipsilateral descending projections from noninvasive brain stimulation (Bradhnam, Stinear, and Byblow 2010; McFarland et al. 2011). However, upregulation of ipsilateral projections from contralesional M1 (cM1) may be an important functional adaptation in patients severely affected by stroke (Ward et al. 2006; Ward et al. 2007). Therefore, contralesional c-tDCS might not benefit this subgroup of patients. This might explain why cM1 suppression has had mixed effects on measures of paretic upper limb function in stroke patients to date. While some studies have shown positive effects on upper limb function (Fregni et al. 2005; Boggio et al. 2007; Grefkes et al. 2010; Kim et al. 2010), others have reported deleterious (Johansen-Berg et al. 2002; Murase et al. 2004; Lotze et al. 2006; Ackerley et al. 2010; Bestmann et al. 2010) or no effects (Talos et al. 2007). These mixed findings indicate it is unlikely that there will be a “one size fits all” strategy for promoting upper limb function after stroke with noninvasive brain stimulation and that the extent to which the cM1 contributes to control of the paretic upper limb needs to be taken into account when selecting protocols for an individual patient. Therefore, the efficacy of contralesional c-tDCS may depend on whether patients are mildly or severely impaired (Schlaug et al. 2008).

This study examined the effects of c-tDCS of cM1 on paretic proximal upper limb muscle activation in patients with subcortical stroke. We hypothesized that because contralesional c-tDCS may suppress ipsilateral descending projections to proximal upper limb, after effects would depend on the relative contribution of cM1 to control of paretic proximal muscles. We predicted that for mildly impaired patients cM1 might interfere with control from the ipsilesional M1 at the level of the spinal cord. Therefore, suppressive tDCS of cM1 was expected to improve the control of the paretic proximal upper limb. Conversely, we predicted that for moderate to severely impaired patients control would be degraded because suppressing cM1 would downregulate ipsilateral compensatory pathways for proximal paretic upper limb control for these patients.

Materials and Methods

Participants

Twelve patients (9 males, mean age 64 ± 3.4 years, range 38–80 years) at least 6 weeks following subcortical cerebral infarction were studied (Table 1). A further 5 patients were assessed but did not meet the
eligibility criteria (see Fig. 1) and were excluded (National Institutes of Health Stroke Scale [NIHSS] < 2 in 4 patients, severe upper limb paresis, 1 patient). Each of the 12 patients was age and gender matched with a healthy adult (mean age 63 ± 3.4 years, range 37 - 79 years, Edinburgh handedness score 0.93 ± 0.05) (Oldfield 1971). Informed consent was given by all participants in accordance with the Declaration of Helsinki. Ethical approval to carry out the study was granted by the regional ethics committee.

**Experimental Design**

The experimental protocol is outlined in Figure 1. Motor impairment and elbow flexor spasticity were assessed in the paretic upper limb using the NIHSS, Fugl-Meyer (FM), and modified Ashworth spasticity scales (ASHs) at an initial screening session. The NIHSS was developed by the National Institutes of Health to assess the severity of stroke. Scores range from 0 to 42, higher scores indicate greater deficiencies. The FM scale is a quantitative measure of sensorimotor impairment, scored of a total of 66, higher scores reflecting less impairment (Brunnstrom 1966). The ASH is a clinical measure of muscle spasticity, scored of 5, higher scores indicate greater spasticity (Bohannon and Smith 1987). Patients attended 2 experimental sessions, separated by 1 week, in which they received either c-tDCS or sham tDCS. Action Research Arm Test (ARAT) scores and corticomotor impairment (Brunnstrom 1966). The ASH is a clinical measure of sensorimotor impairment, scored of 5, higher scores reflecting less impairment (Brunnstrom 1966). The ASH is a clinical measure of sensorimotor impairment, scored of 5, higher scores reflecting less impairment (Brunnstrom 1966). The ASH is a clinical measure of sensorimotor impairment, scored of 5, higher scores reflecting less impairment (Brunnstrom 1966). The ASH is a clinical measure of sensorimotor impairment, scored of 5, higher scores reflecting less impairment (Brunnstrom 1966). The ASH is a clinical measure of sensorimotor impairment, scored of 5, higher scores reflecting less impairment (Brunnstrom 1966). The ASH is a clinical measure of sensorimotor impairment, scored of 5, higher scores reflecting less impairment (Brunnstrom 1966).

**Electromyography**

Surface electromyography (EMG) was recorded from the BB and pronator teres (PT) in the nondominant limb of healthy participants with disposable adhesive electrodes (Ambu, Ballerup, Denmark) placed over the muscle bellies in a bipolar montage. In stroke patients, EMG was recorded from the BB and the PT in the paretic upper limb and from the BB and the first dorsal interosseous (FDI) of the nonparetic limb. EMG signals were amplified (CED 1902, Cambridge, UK), bandwidth filtered (2-1000 Hz), and sampled at 2 kHz (CED 1401, Cambridge, UK).

**Motor Tasks**

Participants performed separate blocks of brief isometric elbow flexion or forearm pronation while seated with their forearm constrained to prevent isometric movement (Gerachshenko et al. 2008; Bradnam, Stinear, and Byblow 2010). Flexor and pronator contractions were paced with an auditory metronome set at a comfortable tempo for each individual (average 0.8 Hz, range 0.6-1 Hz). Participants were instructed to keep pace with the metronome as precisely as possible and to relax completely between contractions. Participants were not asked to produce a particular force but to concentrate on producing a short "burst" of EMG in time with the metronome. Verbal feedback by the experimenter who observed the EMG displayed on the computer screen assisted performance by each individual. Between 20 and 50 repetitions of each task were performed in blocks, with short rests as required. More impaired patients were subject to fatigue and timing errors. The same motor task was used to assess BB motor-evoked potentials (MEPs) in the nondominant arm of control participants who performed 50 repetitions per block paced at 1 Hz, with short rests as required. The aim of the procedure was to obtain at least 10 MEPs per condition/participant for averaging.

**Transcranial Magnetic Stimulation**

Single-pulse TMS was delivered with a figure of 8 coils (70 mm wing diameter) (Magstim Co., Whitland, Dyfed, Wales), positioned over M1 to induce a posterior to anterior directed current in the underlying brain. The 'hotspot' for evoking contralateral MEPs in BB was located for both contralesional and ipsilesional M1 and marked on the scalp. Active motor threshold (AMT) was determined for ipsilesional M1, defined as the minimum stimulus intensity that elicited a 100 μV MEP in 4 of 8 trials during a paretic BB contraction. Contralateral MEPs were obtained in the paretic BB before either rhythmic isometric forearm pronation or elbow flexion, that is, in the resting phase of the task just prior to voluntary contraction. The size of the BB MEP prior to pronation relative to flexion yields a selectivity ratio (SR). BB MEPs are typically smaller prior to pronation than flexion because BB is an antagonist to pronation. The SR therefore reflects the ability to suppress the antagonist and is normally lower in healthy adults than stroke patients (Gerachshenko et al. 2008). Test stimulus intensity was set to 120% of the paretic BB AMT, except in 5 participants who had an AMT above 75% maximal stimulator output (MSO), in which case the test intensity was set to 90% MSO. TMS was timed to occur before the onset of muscle activity (i.e., when the muscle was at rest) during the paced elbow flexion and forearm pronation tasks, between 150 and 250 ms before every fifth metronome beat. For healthy adults, TMS of the nondominant M1 was applied at an intensity of 120% AMT during the same motor tasks and MEPs recorded in the nondominant BB.

The TMS protocol for the patients is summarized in Figure 1. Prior to tDCS and at Postt, single-pulse TMS of cM1 was applied to elicit MEPs in the nonparetic FDI at rest. After tDCS, there was a 5-min consolidation period before FDI MEPs were collected at Postt. MEPs were then elicited for deriving SR (Postt-) using the flexion and pronation
tasks described above. At Post 27, single-pulse TMS of ipsilesional M1 at 80% MSO was used to produce ipsilateral silent periods (iSPs) in the nonparetic BB, while patients maintained isometric elbow flexion at 20% MVC. The intensity was adjusted to produce a 1-mV MEP preintervention. Finally at Post 29, TMS of cM1 at 80% MSO was used to produce ipsilateral MEPs (iMEPs) in the paretic BB, while patients maintained isometric paretic elbow flexion at 20% MVC. Sixteen responses were recorded for each measure described above.

**Transcranial Direct Current Stimulation**

An investigator blinded to all aspects of data collection performed tDCS and investigators responsible for data collection and analysis were blinded to the protocol until study completion. Contralesional c-tDCS was delivered with a constant current of 1 mA for 20 min using a Phoresor II stimulator (Model PM850, IOMED Inc., Utah) via two 35 cm² saline soaked sponge electrodes, with the cathode positioned over the M1 BB hotspot and the anode over the contralateral forehead. This tDCS protocol has been used successfully in studies of stroke patients (Nowak et al. 2009). Sham tDCS was applied with the same configuration, but current intensity was ramped down to zero after 30 s (Gandiga et al. 2006). Following tDCS, patients sat quietly with eyes closed for 5 min to consolidate effects and avoid confounding after effects of stimulation by muscle activity (Huang et al. 2010). Session order was randomized.
Neuroimaging
A Siemens Magnetom Avanto 1.5-T MRI system was used to acquire high-resolution $T_1$-weighted images with a 3D FLASH (fast low angle shot) sequence (time repetition [TR] = 11 ms, time echo [TE] = 4.94 ms, field of view [FOV] = 256 mm, voxel dimensions of $1 \times 1 \times 1$ mm$^3$). DWI was performed with a single shot diffusion-weighted spin echo pulse sequence (TR = 6601 ms, TE = 101 ms, FOV = 230 mm, voxel dimensions of $1.8 \times 1.8 \times 3$ mm$^3$), with diffusion gradients along 30 directions ($b_i = 2000$ s/mm$^2$).

Data Analysis

Selectivity Ratio
BB MEPs for flexion and pronation tasks were rectified and the area (MEP$_{area}$) calculated using the same latency window for each task in each individual. The root mean square EMG (rmsEMG) was calculated within a 100-ms prestimulus window and the time to EMG onset determined. Traces were discarded from each patient’s data if rmsEMG was greater than 1 standard deviation (SD) from the mean rmsEMG for each task or if the agonist EMG onset was less than 70 ms or more than 250 ms after the stimulus. Trials in which MEP$_{area}$ was beyond 2 SDs of the mean were also discarded from further analysis. The remaining trials were averaged to obtain a measure of average BB MEP$_{area}$ for the pronation task and for the flexion task in order to compute the ratio (SR) of the 2 (Gerachshenko et al. 2008). The difference between sham and c-tDCS SR was calculated (ASR = SR$_{sham}$ - SR$_{cDCS}$). A positive ASR indicates selective BB activation was improved by c-tDCS. In healthy participants, EMG data were analyzed as described previously and above, ensuring comparable rmsEMG between flexion and pronation trials for each individual (Bradnam, Stinear, and Byblow 2010).

IMEP and SP Area
IMEP area (IMEP$_{area}$) was determined by rectifying and averaging traces from the paretic BB. IMEP$_{area}$ was calculated in a window 20- to 60-ms poststimulus after the same duration of prestimulus EMG$_{area}$ was subtracted (Bradnam, Stinear, Lewis, et al. 2010). ISP in the nonparetic BB was determined from the rectified and averaged trace. The ISP$_{area}$ relative to the mean of the prestimulus rmsEMG was calculated in a window between 30- and 70-ms poststimulus (Giovannelli et al. 2009).

Image Processing
Image processing was carried out using FSL (FMRI Software Library, Oxford) (Smith et al. 2004; Woolrich et al. 2009). Structural $T_1$-weighted images were skull stripped using the brain extraction tool (BET) (Smith 2002) and used to define the site and size of the brain lesion (Table 1 and Fig. 2). Lesion volume (mm$^3$) was determined by manually tracing lesion masks in FSL-view and calculating mask volume using FSL-stats. DWIs were skull stripped using BET, corrected for motion and eddy currents using FDT (FMRIB’s Diffusion Toolbox) to compute diffusion tensors, and coregistered to the patients $T_1$-weighted image using FLIRT (Smith 2002). ROIs for the left and right posterior limb of the internal capsules (PLICs) were constructed from the JHU DTI-based white-matter labels atlas (Wakana et al. 2007; Hua et al. 2004; Woolrich et al. 2009). An FA asymmetry index was calculated as FA$_{A}$ = (FA$_{c}$ - FA$_{p}$)/(FA$_{c}$ + FA$_{p}$), where FA$_{c}$ = FA in PLIC of contralesional hemisphere and FA$_{p}$ = FA in PLIC of ipsilesional hemisphere, yielding a value between -1.0 and +1.0 for each participant. Zero indicates symmetrical FA in the PLICs and negative and positive values relate to reduced FA in unaffected and affected PLIC, respectively (Stinear et al. 2007). FA$_{A}$ values were calculated for 11 patients (Table 1).

Other Statistical Analyses
The SR was compared between patients after sham tDCS and healthy adults using a 2 sample 2-tailed t test. To determine if SR was influenced by background muscle activity in patients, pre-stimulus rmsEMG and time to EMG burst onset were analyzed using a 2 stimulation (c-tDCS, sham tDCS) x 2 Task (Flexion, Pronation) repeated measures analysis of variance (rmANOVA). As a manipulation check for suppressive effects of cM1 c-tDCS, nonparetic FDI MEP amplitude was measured before, and at 2 time points after, c-tDCS and sham tDCS. Postintervention FDI MEP amplitude was normalized to baseline for each participant. Normalized FDI MEP amplitude was analyzed using 2 stimulation (c-tDCS, sham tDCS) x 2 time (Posts, Post1) rmANOVA. FDI prestimulus rmsEMG was analyzed using a 2 stimulation (c-tDCS, sham tDCS) x 3 time (Pre, Post, Post1) rmANOVA.

Regression analyses were performed to test the hypothesized relationship between the selective paretic BB activation (SR) and the effects of cM1 c-tDCS on selective paretic BB activation (ASR). Regressions were calculated separately for both SR and ASR with measures of time since stroke, NIHSS, ARAT, ASH, FM, FA$_{A}$, lesion size, and c-tDCS SR was calculated (ASR = SR$_{sham}$ - SR$_{cDCS}$). A positive ASR indicates selective BB activation was improved by c-tDCS. In healthy participants, EMG data were analyzed as described previously and above, ensuring comparable rmsEMG between flexion and pronation trials for each individual (Bradnam, Stinear, and Byblow 2010).

Results
There were no adverse events experienced by participants from the study procedures. Anatomical and DWI data were obtained for 11 of 12 patients with one patient unable to fit into the head coil.

Selectivity Ratio
Representative EMG traces for flexion and pronation tasks from 2 patients and 1 healthy adult are shown in Figure 3. Healthy participants completed the task without difficulty. The average burst onset times were $134 \pm 8.9$ and $122 \pm 8.5$ ms for flexion and pronation tasks, respectively. The average prestimulus rmsEMG values were $8 \pm 2$ and $7 \pm 2 \mu$V for flexion and pronation tasks, respectively. For patients, the range of number of trials retained for averaging in the c-tDCS session was 13-19 (flexion) and 10-19 (pronation) and for the Sham session 12-22 (flexion) and 10-18 (pronation), indicating that all subjects were eventually able to complete the required task. The average burst onset times for the c-tDCS session was $145 \pm 8$ (flexion) and $163 \pm 10$ ms (pronation) and for the Sham session $147 \pm 12$ (flexion) and $161 \pm 11$ ms (pronation), with no

![Figure 2. Structural $T_1$-weighted images in the axial plane are shown at the level of the lesion for each patient. Lesions are indicated by the arrows. Patient numbers correspond with Table 1. Note there is no $T_1$-weighted image for patient 3.](image-url)
difference between Session or Task (all \( P > 0.07 \)). The average prestimulus rmsEMG for the c-tDCS session was 15 ± 2 (flexion) and 13 ± 3 μV (pronation) and for the Sham session 16 ± 2 (flexion) and 15 ± 3 μV (pronation). There was no difference between Session and Task (all \( P > 0.16 \)), indicating consistent prestimulus rmsEMG.

The SR reflects the ability to suppress BB prior to pronation, when it is an antagonist. SR data are presented in Table 2 for healthy controls and Table 3 for patients. As expected, SR was higher in patients than healthy adults \((t_{11} = 4.38, P < 0.001)\) reflecting impaired BB suppression. SR correlated negatively with ARAT \((R^2 = 0.83, F_{1,11} = 47.81, P = 0.0001)\) and FM scores \((R^2 = 0.59, F_{1,11} = 14.37, P = 0.004)\). SR correlated positively with ASH \((R^2 = 0.47, F_{1,11} = 8.89, P = 0.014)\) and NIHSS \((R^2 = 0.41, F_{1,11} = 6.93, P = 0.025; \text{Fig. 4A–D})\). SR correlated positively with \(FA_{AI} \) \((R^2 = 0.73, F_{1,10} = 24.68, P = 0.001)\) and lesion size \((R^2 = 0.41, F_{1,10} = 6.21, P = 0.034; \text{Fig. 4E,F})\). SR did not correlate with time since stroke \((P > 0.1)\). Overall, higher SRs were associated with poorer clinical scores and a reduction in the integrity of ipsilesional white matter.

**Effects of c-tDCS on SR (ΔSR)**

The difference between SR measured after sham and after c-tDCS was calculated \((ΔSR = SR_{\text{sham}} - SR_{\text{c-tDCS}})\). As predicted, ΔSR was variable and ranged between -0.37 and 0.32 (Table 3). There was a positive correlation between ΔSR and ARAT \((R^2 = 0.75, F_{1,11} = 29.22, P = 0.0001)\) and between ΔSR and FM scores \((R^2 = 0.59, F_{1,11} = 15.72, P = 0.003; \text{Fig. 5A,B})\). After c-tDCS, SR improved in patients with low ASH, and worsened in patients with ASH > 1, a negative correlation \((R^2 = 0.80, F_{1,11} = 61.65, P = 0.0001; \text{Fig. 5C})\). There was a negative correlation between ΔSR and NIHSS \((R^2 = 0.52, F_{1,11} = 10.71, P = 0.008; \text{Fig. 5D})\). Patients with worse clinical scores had negative ΔSR, indicating worsened control of paretic BB after suppression of cM1 with c-tDCS.

However, SR improved in patients with low FA\(_{AI}\) and worsened in patients with high FA\(_{AI}\) as indicated by a negative correlation \((R^2 = 0.61, F_{1,10} = 14.10, P = 0.005; \text{Fig. 5F})\). Also, SR improved in patients with low baseline SR and worsened in patients with high baseline SR as indicated by the negative correlation \((R^2 = 0.66, F_{1,11} = 19.45, P = 0.001; \text{Fig. 5F})\).

The excitability of the uncrossed corticomotor pathway from cM1 to paretic BB was examined by recording iMEPs. After c-tDCS, SR improved in patients with no iMEPs or small BB iMEP\(_{\text{AREA}}\) and worsened in patients with larger BB iMEP\(_{\text{AREA}}\) indicated by a negative correlation \((R^2 = 0.43, F_{1,11} = 7.46, P = 0.02; \text{Fig. 5G})\). Overall, the ΔSR results indicate that clinical, structural, and neurophysiological measures can predict whether c-tDCS of cM1 will improve or degrade paretic upper limb control.

The iSP is indicative, at least in part, of transcallosal inhibition. There was no correlation between ΔSR and iSP\(_{\text{AREA}}\) \((P = 0.48)\). There was no relationship between ΔSR and time since stroke \((P = 0.17)\). Similarly, there was no relationship between ΔSR and lesion volume \((P = 0.54)\), indicating lesion size did not predict after effects of c-tDCS. Finally, neither lesion size nor handedness was associated with SR or ΔSR.

**Nonparetic FDI MEPS**

MEPs were recorded from nonparetic FDI to confirm that c-tDCS suppressed cM1 excitability. As expected, there was a main effect of stimulation \((F_{1,11} = 9.22, P = 0.011)\) because MEPS were suppressed by c-tDCS in comparison to sham tDCS at 5- and 30-min poststimulation \((P = 0.012 \text{ and } P = 0.017, \text{ respectively})\). One sample \(t\)-tests indicated that after c-tDCS FDI MEP amplitude was reduced compared with baseline at 5 \((–28 ± 0.8\%, P = 0.004)\) and 30 \((–35 ± 0.11\%, P = 0.008)\) min poststimulation. FDI MEP amplitude was comparable prior to c-tDCS and sham stimulation \((P = 0.29)\). EMG levels were consistent during MEP recording with no main effects or interactions for rmsEMG (all \( P > 0.12 \)). Average rmsEMG values were pre: 11 ± 2 μV, post 1: 12 ± 1 μV, and post 2: 13 ± 1 μV. The results for the nonparetic FDI confirm cM1 excitability was suppressed by c-tDCS.

**Discussion**

In support of our hypothesis, suppressive tDCS of cM1 improved the control of the paretic proximal upper limb for...
mildly impaired patients and worsened control for moderate to severely impaired patients. Therefore, protocols for suppressing cM1 are not one size fits all but must be tailored to individual patients.

This is the first study to show that the effects of suppressing cM1 vary depending on the integrity of the white-matter tracts from the ipsilesional hemisphere innervating the paretic upper limb. Suppression of cM1 with c-tDCS worsened paretic upper limb control in patients who had greater impairment and worse damage to their ipsilesional white matter measured at the level of the PLIC. The relationship between ipsilesional white-matter disruption and motor impairment confirm earlier studies that examined paretic hand function after stroke (Ward et al. 2003; Jang et al. 2005; Stinear et al. 2007; Schaechter et al. 2009) and extend this relationship to the neurophysiological response in the paretic proximal upper limb, in response to contralesional c-tDCS. We speculate that significant disruption of ipsilesional motor pathways by stroke would result in greater excitability of the contralesional hemisphere as a compensatory response. In support, functional MRI studies of paretic hand function have found greater lateralization of cortical activity toward cM1 in patients with greater upper limb impairment (Cramer et al. 1997; Ward et al. 2006; Ward et al. 2007; Stinear et al. 2008). In turn, greater contralesional excitability would upregulate

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Note: Stimulus intensity, MEP area for each task, SR, and ΔSR for sham tDCS and c-tDCS are shown for each patient.
activity in the ipsilateral corticobulbospinal projections to the spinal cord, as measured by iMEPs. We found large iMEPs in the paretic BB of our severely impaired patients consistent with previous reports (Turton et al. 1996; Netz et al. 1997; Caramia et al. 2000; Trompetto et al. 2000; Alagona et al. 2001; Gerloff et al. 2006; Lewis and Perreault 2007), although to some extent the significant relationship with ASR was driven by the 2 most impaired patients. Although the effects of c-tDCS on direct ipsilateral projections to the spinal cord are inconclusive, the current findings indicate that suppression of cM1 may be contraindicated for patients with major disruption of the ipsilesional corticospinal tract, as this may result in down-regulation of important compensatory activity.

Conversely, these results indicate that suppression of cM1 may be beneficial in patients with residual structural integrity of the ipsilesional hemisphere. These patients had less damage to ipsilesional motor pathways with lower FA asymmetry of the PLICs, better clinical scores, and more selective control of the paretic upper limb. cM1 may not therefore be required for compensation in these patients, and its ipsilateral projections may even interfere at the spinal level with the control of paretic proximal muscles by ipsilesional M1. The benefits of cM1 c-tDCS for paretic upper limb control in mildly impaired patients were unlikely to result from a reduction in transcallosal inhibition. This is because no correlation between changes in the SR following c-tDCS and the iSP was found. The iSP is considered, at least in part, to measure transcallosal inhibition across the corpus callosum (Chen 2004; Trompetto et al. 2004; Avanzino et al. 2007). In more severely affected patients, improvements in upper limb impairment have been associated with reduced transcallosal inhibition from the contralesional to the ipsilesional hemisphere (Harris-Love et al. 2011). However, there was no evidence for decreased transcallosal inhibition in the current study, perhaps because

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**Figure 5.** Regressions with ΔSR. Positive ΔSR indicates improved selective muscle activation after contralesional c-tDCS and negative ΔSR indicates a worsening of selective muscle activation after contralesional c-tDCS. The dashed line represents no change, ΔSR = 0. (A) ΔSR and ARAT. SR improved for those with mildly impaired upper limb function worsened for those with ARAT scores < 40. (B) ΔSR and FM score. SR tended to improve for patients with mild upper limb impairment and worsen for those with FM < 50. (C) ΔSR and ASH. SR tended to improve for patients without elbow flexor spasticity and worsen for those with ASH > 1. (D) ΔSR and NIHSS. SR tended to worsen for patients with NIHSS of 5 or more. (E) ΔSR and FA_AL. SR tended to improve for patients with good ipsilesional corticospinal tract integrity. (F) ΔSR and SR. SR tended to improve in those with good initial selective muscle activation and worsen for those with poor initial selective muscle activation. (G) ΔSR and iMEP_area. SR tended to improve for patients with small iMEPs in the paretic BB and worsen for those with large iMEPs. All other abbreviations as in text.
there was no repetitive motor training involved in the current study (Harris-Love et al. 2011). A more likely explanation is that c-tDCS suppressed ipsilateral corticomotor projections, thereby reducing interference with contralateral inputs at the spinal level for patients with mild upper limb impairment. Therefore, suppression of cM1 may be beneficial in patients with mild proximal upper limb weakness. This extends previous studies, which found that cM1 c-tDCS enhanced paretic hand function in mildly affected patients (Fregni et al. 2005; Boggio et al. 2007; Kim et al. 2010).

Although noninvasive brain stimulation may be used to promote balanced motor cortex excitability after stroke, there is still debate as to whether suppression of cM1 or facilitation of ipsilesional M1 is the more efficacious approach (Hummel and Cohen 2006; Hummel et al. 2008; Bolognini et al. 2009; Nowak et al. 2010). Differences in the contribution of cM1 to control of the paretic upper limb may explain why noninvasive brain stimulation has generally yielded mixed results in patients after stroke. For example, suppression of cM1 with repetitive TMS was found to degrade performance of a grip-lift task in stroke patients (Ackerley et al. 2010). Suppression of M1 using similar techniques may also impair ipsilateral upper limb function, motor learning, and skill retention in healthy adults (Chen et al. 1997; Carey et al. 2006; Bradnam, Stinear, and Byblow 2010). Further studies might well examine the effect of noninvasive brain stimulation on the control of distal and proximal muscles, in both the contralateral and the ipsilateral upper limb.

Neurophysiological and neuroimaging measures can be used to predict current functional status and functional recovery following stroke (Le Bihan et al. 2001; Stinear et al. 2007; Schaechter et al. 2009; Lindenberg et al. 2010; Radlinska et al. 2010; Zhu et al. 2010; Qiu et al. 2011) and may be useful to select patients who are suitable for specific protocols. In this study, measures of structural integrity of descending white-matter tracts predicted upper limb function, alongside clinical assessments. FA asymmetry measured in the PLICs predicted after effects of c-tDCS on SR, whereas lesion size did not. The finding that FA within the posterior limbs of the internal capsules can be used to predict upper limb function is in agreement with previous studies (Cramer et al. 2007; Stinear et al. 2007; Qiu et al. 2011; Riley et al. 2011) and reinforces the importance of the ipsilesional corticofugal pathways in stroke recovery. The present findings indicate FA asymmetry measures may also assist in selection of noninvasive brain stimulation protocols for individual stroke patients (Cramer 2010; Stinear 2010).

This study has several limitations that must be considered when interpreting the results. First, the stimulus intensity for tDCS cannot be individualized based on motor thresholds as for repetitive TMS (Priori et al. 2009) and may produce variable effects between individuals. Secondly, the cathode may hyperpolarize cortical areas adjacent to M1 (Nitsche et al. 2007). The dorsal premotor cortex may also have been modulated by c-tDCS (Boros et al. 2008). The contralesional premotor cortex is known to have a compensatory role in promoting upper limb function in more impaired patients (Johansen-Berg et al. 2002; Gerloff et al. 2006; Lotze et al. 2006; Ward et al. 2006; Bestmann et al. 2010). We cannot know if the decrement in paretic upper limb control in our moderate to severely affected patients was due to suppression of neurons within dorsal premotor cortex alongside those within M1. This may be problematic for selecting brain stimulation protocols to target the proximal paretic upper limb, as the representation of proximal muscles relative to distal muscles is greater in dorsal premotor cortex (Dum and Strick 1991). Further studies are needed to determine relative effects of “direct” dorsal premotor cortex tDCS with M1 tDCS on proximal paretic upper limb function. Third, the small number of participants may have influenced the neuropsychological results, which indicated that the effects of cM1 c-tDCS were mediated by ipsilateral rather than transcallosal projections. However, iMEP and iSP measures are variable and are not present in all healthy individuals or stroke patients (Chen et al. 2003; Talelli et al. 2006), making it difficult to precisely determine the pathways mediating effects on the ipsilateral side of the body. The effects of M1 tDCS on paretic arm control may be secondary to changes in transcallosal inhibition (Nowak et al. 2010). Further investigations are required to determine the relative effects of suppressive stimulation on ipsilateral corticomotor and transcallosal pathway excitability. Fourth, because the strength of stimulation was necessarily higher for patients than healthy control subjects, the extent of activation depth or spread between groups may have contributed in part to the difference in SR between groups. However, this would not affect ASR, the outcome measure of interest. A final limitation is the lack of outcome measures that specifically assess proximal paretic upper limb control. The ARAT was used in the current study, but primarily tests skills associated with using the hand and scores are not sensitive to improvements in proximal upper limb control (Lyle 1981). Development of a validated outcome measure specific to proximal upper limb function in stroke patients would improve future studies. Despite these limitations, this study has highlighted factors worthy of consideration before using noninvasive brain stimulation for rehabilitation after stroke.

There is unlikely to be a one size fits all treatment protocol when using noninvasive brain stimulation in stroke rehabilitation. We have shown that c-tDCS of cM1 may be beneficial for patients with mild impairment and contraindicated for patients with moderate to severe impairment. An important clinical aspect of the present study is that clinical measures of upper limb function and impairment, and spasticity in the paretic elbow flexors, may be useful for determining whether contralesional c-tDCS is contraindicated for an individual patient. Future experiments may identify how to individually prescribe tDCS as an adjuvant to therapy.

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