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Inhibition versus facilitation of contralesional motor cortices in stroke: Deriving a model to tailor brain stimulation

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Abstract

Objective—The standard approach to brain stimulation in stroke is based on the premise that ipsilesional M1 (iM1) is important for motor function of the paretic upper limb, while contralesional cortices compete with iM1. Therefore, the approach typically advocates facilitating iM1 and/or inhibiting contralesional M1 (cM1). But, this approach fails to elicit much improvement in severely affected patients, who on account of extensive damage to ipsilesional pathways, cannot rely on iM1. These patients are believed to instead rely on the undamaged

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Conflict of interest

Andre G. Machado has the following conflict of interests to disclose: being a consultant of functional neuromodulation at St Jude; having distribution rights at Enspire, ATI, and Cardionomics; having fellowship support from Medtronic. Unrelated to present work, Adriana B. Conforto has the following conflict of interests to disclose: as a consultant at BMS/Pfizer and Bayer. Other authors have no conflict of interests to disclose.

cortices, especially the contralesional dorsal premotor cortex (cPMd), for support of function of the paretic limb. Here, we tested for the first time whether facilitation of cPMd could improve paretic limb function in severely affected patients, and if a cut-off could be identified to separate responders to cPMd from responders to the standard approach to stimulation.

Methods—In a randomized, sham-controlled crossover study, fifteen patients received the standard approach of stimulation involving inhibition of cM1 and a new approach involving facilitation of cPMd using repetitive transcranial magnetic stimulation (rTMS). Patients also received rTMS to control areas. At baseline, impairment [Upper Extremity Fugl-Meyer (UEFM_{PROXIMAL}, max =36)] and damage to pathways [fractional anisotropy (FA)] was measured. We measured changes in time to perform proximal paretic limb reaching, and neurophysiology using TMS.

Results—Facilitation of cPMd generated more improvement in severely affected patients, who had experienced greater damage and impairment than a cut-off value of FA (0.5) and UEFM_{PROXIMAL} (26–28). The standard approach instead generated more improvement in mildly affected patients. Responders to cPMd showed alleviation of interhemispheric competition imposed on iM1, while responders to the standard approach showed gains in ipsilesional excitability in association with improvement.

Conclusions—A preliminary cut-off level of severity separated responders for standard approach vs. facilitation of cPMd.

Significance—Cut-offs identified here could help select candidates for tailored stimulation in future studies so patients in all ranges of severity could potentially achieve maximum benefit in function of the paretic upper limb.

Keywords

Diffusion tensor imaging; Motor cortex; Premotor cortex; Neuronal plasticity; Rehabilitation; Stroke; Transcranial Magnetic Stimulation

1. Introduction

Stimulation of the brain is a well-accepted experimental technique for promoting recovery of the paretic upper limb after stroke. Based on the premise that ipsilesional primary motor cortex (iM1) is important for motor function (Nudo et al., 1996) and contralesional motor cortices compete with iM1 to inhibit output devoted to the paretic upper limb (Murase et al., 2004), the standard approach involves facilitating iM1 and/or inhibiting the contralesional motor cortices (Fregni et al., 2007, Di Lazzaro et al., 2013). However, this approach fails to generate much improvement in severely affected patients (Malcolm et al., 2007, Ackerley et al., 2010, Hesse et al., 2011, Talelli et al., 2012, Levy et al., 2015). These patients sustain extensive damage to ipsilesional pathways (Hedna et al., 2013), so emphasizing iM1 is less likely to affect function of the paretic upper limb (Nouri et al., 2011, Levy et al., 2015, Simis et al., 2016). Instead, undamaged cortices, especially the contralesional dorsal premotor cortex (cPMd) may offer support (Johansen-Berg et al., 2002, Ackerley et al., 2010, Bradnam et al., 2012). Inhibition of cPMd (more than inhibition of any other contralesional region) impairs movement of the paretic limb in severely affected patients, suggesting that

plasticity of cPMd makes causal contribution to their function of the paretic limb. cPMd is believed to support function by alleviating competition imposed on iM1 (Johansen-Berg et al., 2002, Bestmann et al., 2010, Chen et al., 2016, Mohapatra et al., 2016). Therefore, a more recent hypothesis suggests that undamaged areas like cPMd are key for recovery of severely affected patients, while iM1 is important only for mildly affected (Di Pino et al., 2014, Plow et al., 2016). This hypothesis is also referred to as the “bimodal hypothesis” of plasticity.

While it would seem logical to tailor stimulation according to the bimodal hypothesis of plasticity, several challenges remain. It is unclear what cut-off separates mildly affected patients from severely affected patients for application of tailored stimulation to iM1 and undamaged, contralesional cortices, respectively. Given that contralesional cortices have not been previously facilitated in humans, it is also unknown whether facilitating cPMd or facilitating other contralesional regions, like contralesional M1 (cM1) (Carmel et al., 2014, Buetefisch, 2015, Yao et al., 2015), would be more effective to support function in severely affected patients. Last, would stimulating contralesional cortices be even more effective than stimulating higher-order ipsilesional cortices, like ipsilesional PMd (iPMd) which may assume the role of iM1 in patients with severe damage (Carey et al., 2002, Ward et al., 2003a, Dancause et al., 2011, Ward, 2011)?

To address these questions, we performed a series of randomized, sham-controlled, crossover experiments. In the main experiment, patients received stimulation based on a standard approach (inhibition of cM1), and stimulation that involved facilitation of cPMd, in line with the bimodal hypothesis. We measured change in time to perform proximal reaching at the paretic upper limb to index improvement in function (Harris-Love et al., 2011) and change in neurophysiology to index plasticity associated with stimulation. At baseline, we assessed impairment using a common clinical scale (Fugl-Meyer et al., 1975) and damage to pathways using diffusion tensor imaging (DTI) (Stinear et al., 2007) and transcranial magnetic stimulation (TMS) (Rossini et al., 1994). We hypothesized that as baseline damage/impairment would become severe, patients would fail to improve with the standard approach involving inhibition of cM1, and instead improve with stimulation facilitating cPMd. Since the relationship between damage/impairment and change in proximal reaching associated with both techniques would be opposite, we anticipated intersection of their regression curves would serve as the cut-off value of severity that separates patients responding to standard inhibition of cM1 from patients responding to facilitation of cPMd. We also anticipated that responders to standard cM1 inhibition technique would experience gains in ipsilesional output with improvements in proximal reaching, while responders to cPMd facilitation would show alleviation of competition imposed on iM1 from contralesional cortices.

In a separate experiment, a subset of patients with severe ipsilesional damage also received stimulation to facilitate cM1 in order to help understand whether stimulating cPMd or cM1 elicits more improvement in severely affected patients. We anticipated greater improvements with facilitation of cPMd, in association with greater reduction in competition imposed on iM1.

In another control experiment, patients additionally received stimulation of iPMd. We tested the hypothesis that as baseline damage/impairment would become severe, patients would fail to improve with the standard approach involving inhibition of cM1 and improve instead with stimulation facilitating iPMd. If, however, patients who fail to improve with inhibition of cM1 also fail to improve with stimulation of iPMd, but show improvement with stimulation of cPMd, then the bimodal hypothesis— that contralesional (not ipsilesional) motor cortices are more important for severely affected patients— would be validated.

2. Methods

2.1 Subjects

We enrolled 15 patients 21 years of age who had experienced first-ever unilateral ischemic stroke 6 months prior to enrollment. Patients with hemorrhagic stroke were included if their lesion affected subcortical territories similar to those affected typically in ischemic stroke [for example, posterior limb of the internal capsule (PLIC)] (Hedna et al., 2013). We anticipated that if location of lesion following a hemorrhage were not different from location of lesion that typically follows an infarct, then the confounding effect of lesion type would be mitigated.

All patients showed weakness of the upper limb and 20% slowness in reaching with the paretic vs. the nonparetic limb (Harris-Love et al., 2011). We excluded patients with severe cognitive dysfunction (< 24 on the Mini-Mental State Examination, MMSE) (Folstein et al., 1983) or other neurologic/psychiatric illnesses or contraindication to TMS or magnetic resonance imaging (MRI) (Rossi et al., 2009). Patients were also excluded on account of participation in recent (< 3 months) or ongoing physical/occupational therapy or an inability to perform reaching with the paretic limb. All study procedures were in accordance with the declaration of Helsinki (1964). All patients provided written informed consent.

2.2 Baseline Assessments

At baseline, we measured impairment of the paretic limb using the Upper Extremity Fugl-Meyer (UEFM) scale (Fugl-Meyer et al., 1975). UEFM tests 33 movements, rated on an ordinal scale (0–2). The maximum score (UEFM_{TOTAL}) is 66; lower scores reflect greater impairment (Berglund et al., 1986). The maximum score for the proximal upper limb (UEFM_{PROXIMAL}) is 36; that for the distal upper limb (UEFM_{HAND}) is 30. UEFM has acceptable inter-rater reliability and concurrent validity (Berglund et al., 1986).

We measured structural damage to ipsilesional pathways using DTI (Stinear et al., 2007, Lindenberg et al., 2010). DTI was acquired on a 3T Siemens Trio (Siemens Medical Systems, Erlangen, Germany) using 71 diffusion-weighting gradients ($b = 1000 \text{ s/mm}^2$) and 8 image volumes ($b = 0 \text{ s/mm}^2$). Total scan time was 12 minutes. (Cunningham et al., 2015a). Acquisition provided whole-brain coverage using 2-mm isotropic voxels (field of view: $256 \times 256 \text{ mm}$, image matrix: 128×128 and 52 2-mm-thick slices).

We measured physiologic damage to ipsilesional pathways using single-pulse TMS (Rossini et al., 1994). TMS was delivered using a figure-of-eight coil (70 mm diameter) connected to a monophasic stimulator (200², Magstim Co. Ltd., UK). The coil was oriented tangentially

to the scalp, with the handle oriented backward and laterally at a 45° angle from midline. As such, the coil aligned approximately perpendicular to the line of the central sulcus. This orientation includes a posterior-anterior current in the brain, which requires pulses of lower intensity for activation (Brasil-Neto et al., 1992, Mills et al., 1992).

Functional MRI (fMRI) activation was used for stereotactic guidance of TMS (Brainsight, Rogue Research Inc., Montreal, QC, Canada) (Cunningham et al., 2015a). fMRI guidance is helpful because patients with chronic stroke undergo cortical reorganization (Lotze et al., 2003, Ward et al., 2003a, Ward et al., 2006). As such, anatomical localization that relies on identifying the hand knob area or 10–20 EEG landmarks becomes less accurate. fMRI maxima can help localize reorganized territory within M1 that is activated in association with movement of the paretic hand (Lotze et al., 2003, Diekhoff et al., 2011). Stereotactic mapping grids (3 × 5) were centered at the site of fMRI activation maxima (Potter-Baker et al., 2016). All sites within the mapping grid were targeted with TMS using stereotactic navigation, while motor-evoked potentials (MEPs) were recorded (PowerLab 4/25T, AD Instruments, Colorado Springs, CO) from the paretic extensor digitorum communis (EDC) muscle using surface electromyography (EMG) electrodes (silver-silver chloride, 45 mm diameter). A reference electrode was placed over the clavicle. “Motor hotspot” was identified within the region of iM1 as the site evoking MEPs of at least 100 µV peak-to-peak amplitude in slightly contracted paretic EDC (20%–50% of maximum volitional contraction) in at least 3 of 5 trials at the lowest TMS intensity (Rossini et al., 2015). The intensity used to elicit criterion-level MEPs was called the active motor threshold (AMT) (Pennisi et al., 1999).

2.3 Design and Procedures

One week after baseline assessments, patients participated in an overall single blind, sham-controlled, crossover study. The study comprised of several experiments, involving stimulation of various motor cortical areas (Fig. 1). Sessions were presented in a randomized order and separated by 1 week to allow for washout (Mansur et al., 2005, Khedr et al., 2007).

Stimulation was applied using repetitive TMS (rTMS) delivered using a figure-of-eight coil (70 mm diameter) (MagVenture, MagPro R30, Denmark) (Khedr et al., 2007, Carey et al., 2008). Again, the coil was placed tangentially to the scalp, with the handle oriented backward and laterally at a 45° angle from midline. MRI-based frameless stereotaxy was used again to guide the application. Biphasic pulses with a pulse width of approximately 300µsec were delivered using rTMS.

For the main experiment, patients received stimulation based on the standard approach that involved inhibition of cM1, and stimulation based on the bimodal hypothesis that involved facilitation of cPMd. We chose to inhibit cM1 as part of the standard approach because it is the most commonly used technique to facilitate excitability of iM1 (Fregni et al., 2006, Carey et al., 2008, Di Lazzaro et al., 2008). CM1 was inhibited using 1 Hz rTMS (3 trains of 500 pulses each, 1500 pulses total, 25 minutes). Motor hotspot was localized based on MEPs evoked in the nonparetic EDC (similar to description provided above for identifying motor hotspot in iM1). Stimulation was delivered at an intensity of 90% AMT. CPMd was

facilitated using 5 Hz rTMS (5 trains of 300 pulses each, 1500 pulses total, 10 minutes) (Rizzo et al., 2004). CPMd was localized to a site ≈ 2.5 cm anterior to cM1 using MRI-based stereotaxy (Rizzo et al., 2004). Offline analysis using Brainsight and AFNI (<http://afni.nih.gov/afni/>) confirmed that coordinates of cM1 and cPMd indeed were separated by 2.51 ± 1.01 cm. Stimulation was delivered at an intensity of 90% AMT based on safety recommendations for high-frequency rTMS (Wassermann, 1998) and methods adopted in other studies (Gerschlag et al., 2001). Similar to other studies, AMT was defined based on the hotspot in cM1, a strategy that helps avoid the spread of current from PMd to the posteriorly located M1 (Baumer et al., 2003). As part of a sub-experiment, a subset ($n = 5$) of severely affected patients who could not evoke any MEP in the paretic EDC with TMS additionally received stimulation involving facilitation of cM1. cM1 Same parameters were used as used for facilitation of cPMd.

As part of a control experiment, patients also received stimulation involving facilitation of iPMd. IPMd was localized to a site ≈ 3 cm anterior to iM1 using MRI-based stereotaxy (Boros et al., 2008, Cunningham et al., 2015b). Offline analysis confirmed that coordinates of iM1 and iPMd were indeed separated by 2.47 ± 1.12 cm. IPMd too was facilitated using the same parameters as those used for facilitation of cPMd. Stimulation was delivered at an intensity of 90% AMT. Only in instances where AMT could not be determined due to absence of MEPs in the paretic limb, iPMd was stimulated at 90% of maximum stimulator output (% MSO).

Sham rTMS was applied using the same coil that applies real rTMS. The coil offers real stimulation on one side and sham stimulation on the other (MagVenture A/P coil). The goal is to elicit similar perceptions and auditory sensations to facilitate patient blinding.

2.4 Outcomes

We recorded time to perform proximal reaching at the paretic upper limb, termed here as (“reaching time” [RT]; Fig. 1) (Harris-Love et al., 2011). Patients were seated comfortably in a high-back chair. Trunk movements were restrained using elastic straps. On a table in front of the patient, three response buttons (3 cm height), labeled 1, 2 and 3, were arranged in a semicircle at 80% of maximum voluntary reaching distance of the paretic upper limb (Fig. 2A) (Harris-Love et al., 2011). A start button was placed at the center of the semicircle at the edge of the table. Patients rested their test hand on the start button. A computer screen displayed a number that corresponded to the number of the button that the patients were required to reach and push. This visual cue was followed immediately by an auditory beep. At the sound of the beep, patients reached forward and firmly pressed the cued button, and the remaining buttons (direction: clockwise for right hand, counter-clockwise for left hand). We tested paretic and nonparetic limbs separately and in a random order. We completed a minimum of 20 trials per limb (two blocks of 10 trials each, with an ~ 60 s interval between blocks) before and after each session of rTMS. We noted RT (in ms) as the time required to push the cued button and serial RT as that required to press all buttons. Patients were familiarized with the RT task at baseline assessment, during which they performed 3 blocks of 10 trials each (Fig. 1).

2.5 Neurophysiology

We studied changes in corticospinal output, and interhemispheric inhibition imposed on iM1 from contralesional motor cortices (Fig. 1, 2B). Corticospinal output was recorded from both iM1 and cM1. Ten serial MEPs each were recorded in contracted, contralateral EDC muscle (during 20%–50% of maximum volitional contraction) at different intensities of TMS, ranging from 90 to 150% AMT (Fig. 2B) (Devanne et al., 1997). Intensities were presented in a randomized order. EMG was amplified (X500–5000), band-pass filtered (10 Hz–2 kHz) and digitized at 4 kHz (Cunningham et al., 2016). Inter-hemispheric inhibition was measured by applying TMS to cM1 during 50% maximum volitional contraction of the paretic EDC (10 pulses at 150% AMT) (Harris-Love et al., 2011). TMS-induced suppression of ongoing EMG or “silence” in the ipsilateral paretic EDC was detected (Fig. 2B). EMG was digitized at 2 kHz (Garvey et al., 2001). Digitized EMG responses were analyzed offline using LabChart Pro (version 7.3; AD Instruments Inc., Colorado Springs, CO).

2.6 Data Analysis

Lesion locations were defined on T1-weighted images by a trained neurologist (Supplementary Figure S1). Lesion volumes were defined using MRicro (CRNL, University of South Carolina, Columbia, SC; <http://www.mccauslandcenter.sc.edu/mricro/>; (Table 1A) (Zhu et al., 2010). DTI images were corrected for eddy currents and head motion using FSL (Analysis Group, Centre for Functional MRI of the Brain, Oxford, UK). Whole-brain diffusion tensor maps of fractional anisotropy (FA) were calculated. We applied a threshold value of FA = 0.2 (Lindenberg et al., 2010, Zhu et al., 2010). We studied damage at the level of the PLIC because it represents a major convergence point for corticospinal tracts to the upper extremity (Stinear et al., 2007). We defined PLIC across three consecutive slices centered at the appropriate level of the foramen of Monro on the axial plane of the FA map (b0 space) (Sidaros et al., 2008, Puig et al., 2011). We determined FA at ipsilesional PLIC (Mean FA). Lower values of mean FA indicate severe structural damage (Table 1A).

We indexed physiologic damage to ipsilesional pathways using MEPs. We converted MEPs into a dichotomous variable, since many patients with severe damage were unable to evoke MEPs even at 100% MSO (Stinear et al., 2007). These patients were categorized as “MEP_{ABSENT}”, while patients who could evoke MEPs were categorized as “MEP_{PRESENT}” (Table 1A).

We defined RT (ms) as the time interval between the sound of the auditory beep and the time-point at which patients pressed the cued button. Serial RT (ms) was defined as the total time required to press all buttons. Since patients with greater impairments were only able to press the first cued button, we did not include serial RT in the final analysis. We computed “Change in RT performance” from pre- to post-rTMS. “Change in RT performance” was always expressed relative to the change with sham.

Corticospinal output was defined using MEPs collected at supra-threshold TMS intensities. Since intensity that generates maximum MEP varies from patient to patient (Rossini et al., 2007), we identified such intensity based on individual input-output curves. The input-output curves were plotted intensity (90% to 150% AMT) vs. MEP size, noted as peak-to-peak

amplitude (normalized to values of EMG generated during maximum volitional contraction) (Fig. 2B). We noted amplitude of (normalized) MEP at the point of maximum gain in the input-output curve. We computed percent change in amplitude of this normalized MEP from pre- to post-rTMS (Fig. 2B; Equation 1).

$$\text{Corticospinal output} = \left[\frac{\text{Post MEP} - \text{Pre MEP}}{\text{Pre MEP}} \right] * 100 \quad \text{Equation 1}$$

Interhemispheric inhibition was defined by calculating TMS-induced suppression of EMG in the ipsilateral paretic EDC; the period of suppression is commonly referred to as the ipsilateral silent period (iSP) (Chen et al., 2003, Harris-Love et al., 2011). Onset of iSP was defined when EMG of the contracting paretic EDC fell below 1 standard deviation of prestimulus EMG for 5 ms; the offset was defined when EMG returned within 1 standard deviation for 3 ms (Chen et al., 2003). We calculated percent change in iSP relative to mean prestimulus EMG (Equation 2). We then computed percent change in iSP from pre- to post-rTMS (Fig. 2B).

$$\text{Interhemispheric inhibition} = \left[\frac{\text{Mean prestimulus EMG} - \text{iSP EMG}}{\text{Mean prestimulus EMG}} \right] * 100 \quad \text{Equation 2}$$

2.7 Statistical Analysis

We tested normality of data using the Shapiro-Wilk test. Between- and within-session reliability of RT and neurophysiologic variables was tested using paired *t* tests, one-way repeated-measures analysis of variance, and intra-class correlation coefficient (ICC), as appropriate.

We identified several key predictors of change in RT performance, including lesion volume, lesion location, MMSE, FA, UEFM, MEP_{ABSENCE} or MEP_{PRESENCE} and clinico-demographic variables, such as age, gender, handedness, side of paresis and time since stroke (Table 1B). We determined which of these predictors shared a significant relationship (Pearson's correlation) with change in RT performance associated with standard inhibition of cM1 and cPMd facilitation. We included only those predictors in subsequent regression analyses, which showed significant correlation with change in RT performance associated with both techniques.

For the main experiment, we used bivariate linear regression to study how change in RT performance associated with standard inhibition of cM1 vs. cPMd facilitation varied with baseline predictors of damage and impairment. We specifically examined whether with greater damage and impairment, standard inhibition of cM1 elicited little to no change in RT performance ($\beta_{\text{standard}} = 0$), and cPMd facilitation elicited greater improvement in RT performance ($\beta_{\text{cPMd}} = 0$). If the relationships indeed were opposite, i.e., $\beta_{\text{standard}} = 0$ and $\beta_{\text{cPMd}} = 0$, then we anticipated identifying cut-offs using Classification and Regression Tree (CART) analysis (Breiman et al., 1984). CART can calculate cut-offs based on β -weights of individual predictors. Based on cut-offs, CART plotted a decisional algorithm that stratified

candidates for tailored stimulation (standard cM1 inhibition vs. cPMd facilitation). Again, for the main experiment, we used bivariate correlation to study how change in RT performance associated with both techniques varied with corresponding changes in neurophysiology.

For the control experiment as well, we used bivariate linear regression to study how change in RT performance associated with standard inhibition of cM1 vs. iPMd stimulation varied with baseline damage and impairment.

Finally, for comparing RT performance and changes in neurophysiology associated with cPMd vs. cM1 facilitation, we employed the nonparametric Wilcoxon signed-rank test. Significance levels were set at $P = 0.05$. Statistical analysis was performed using SPSS (v18, SPSS Inc., Chicago, IL).

3. Results

All patients completed rTMS, and there were no adverse events. One patient could not undergo MRI due to claustrophobia. Patients were typically slower upon RT performance of the paretic limb than the nonparetic limb ($t_{14} = 5.274$, $P = 0.001$). Patients who were more impaired (UEFM_{TOTAL}) were especially slower ($r = 0.67$, $P = 0.035$) (Supplementary Figure S2A).

RT of paretic and nonparetic limbs showed excellent between-session reliability [$(F_{2,28} = 1.204$, $P = 0.315$; $ICC_{3,1} = 0.91$); ($F_{2,28} = 0.863$, $P = 0.433$; $ICC_{3,1} = 0.88$), respectively] (Supplementary Figure S2C). RT also showed excellent within-session reliability with sham rTMS [$(t_{14} = -0.671$, $P = 0.513$; $ICC_{3,1} = 0.99$); ($t_{14} = -1.001$, $P = 0.334$; $ICC_{3,1} = 0.95$), respectively] (Supplementary Figure S2D). MEPs of paretic and nonparetic limbs also showed excellent within-session reliability [$(t_8 = -0.847$, $P = 0.422$; $ICC_{3,1} = 0.72$); ($t_{14} = 0.074$, $P = 0.942$; $ICC_{3,1} = 0.98$), respectively] and similarly interhemispheric inhibition imposed on iM1 did not change with sham rTMS ($t_{14} = -0.989$, $P = 0.339$; $ICC_{3,1} = 0.97$).

3.1 Main experiment

Of all independent variables collected at baseline (Table 1B), only UEFM_{PROXIMAL}, mean FA, and MEP were significant predictors of change in RT performance associated with standard inhibition of cM1 and cPMd facilitation. These predictors were entered into subsequent regression analyses. As UEFM_{PROXIMAL} and mean FA values became more severe, standard inhibition of cM1 elicited little to no change in RT performance [$(r = -0.60$, $P = 0.015$, 95%CI = -0.85 to -0.13); ($r = -0.61$, $P = 0.01$, 95%CI = -0.71 to 0.29)], whereas cPMd facilitation elicited significant improvement [$(r = 0.90$, $P = 0.001$, 95%CI = 0.72 to 0.97) and ($r = 0.72$, $P = 0.002$, 95%CI = 0.36 to 0.92)] (Fig. 3A, B). Since UEFM_{PROXIMAL} and mean FA shared opposite relationships with change in RT associated with both techniques, we were able to identify cut-off values of UEFM_{PROXIMAL} and mean FA (23 and 0.46, respectively) that separated responders to standard inhibition of cM1 from responders to cPMd facilitation (Fig. 3A, B).

CART served to offer more definitive cut-offs and a decisional algorithm. Patients who were more severely impaired than $UEFM_{\text{PROXIMAL}} = 26$ were deemed responders to cPMd stimulation. Patients who were less impaired ($UEFM_{\text{PROXIMAL}} > 26$) were studied further based on values of mean FA and $UEFM_{\text{PROXIMAL}}$. Patients with mild damage to pathways (mean FA > 0.5), were found to be responders to standard cM1 inhibition, but patients with more serious impairment ($UEFM_{\text{PROXIMAL}} < 28$) and significant damage (mean FA < 0.5) were evidenced to be responders to cPMd facilitation (Fig. 3D).

Although patients with severe physiologic damage (MEP_{ABSENT} seemed to respond more to cPMd facilitation than standard cM1 inhibition, and patients with less damage (MEP_{PRESENT}), seemed to improve more with standard cM1 inhibition than cPMd facilitation, these findings were not significant ($P = 0.234$, $P = 0.116$) (Fig. 3C). Therefore, MEP was not entered into the CART analysis and the decisional algorithm described above.

Our sub-experiment demonstrated that responders to cPMd who were severely affected (MEP_{ABSENT}) tended to improve more with cPMd than with cM1 facilitation ($z = -1.83$, $P = 0.06$) (Fig. 4A). Neurophysiological findings revealed that facilitation of cPMd likely generated greater reduction in iSP than facilitation of cM1 ($z = -1.83$, $P = 0.06$) (Fig. 4B).

3.1.1 Neurophysiology—As anticipated, following standard inhibition of cM1 patients demonstrated a decrease in nonparetic MEPs ($t_{14} = 5.062$, $P < 0.001$). However, they failed to demonstrate consistent increases in paretic MEPs. While patients with mild physiologic damage (low AMT) experienced notable increases, patients with severe damage (high AMT) experienced no gains ($r = -0.64$, $P = 0.05$) (Fig. 5A). Evidence of increase in paretic MEPs was associated with improvement in RT performance ($r = 0.36$, $P = 0.034$), i.e., patients who showed increase in amplitude of paretic MEPs after standard inhibition of cM1 also improved upon RT (Fig. 5B).

Following cPMd facilitation, patients demonstrated an increase in nonparetic MEPs, as anticipated ($t_{14} = -2.685$, $P = 0.018$). However, they failed to demonstrate any increase in paretic MEPs, even though they experienced a reduction in iSP or interhemispheric inhibition imposed on iM1 ($t_{14} = -1.34$, $P < 0.001$). Reduction in iSP was marked in severely impaired patients, while mildly affected patients witnessed no remarkable change ($r = 0.70$, $P < 0.001$) (Fig. 5C). Evidence of reduction in iSP was associated with improvement in RT performance ($r = 0.75$, $P < 0.001$), i.e. patients who experienced greater reduction in iSP also improved upon RT after cPMd facilitation (Fig. 5D).

3.2 Control experiment

As $UEFM_{\text{PROXIMAL}}$ and mean FA values became more severe, standard inhibition of cM1 elicited little to no improvement in RT performance [$(r = -0.60$, $P = 0.015$, $95\% \text{CI} = -0.85$ to -0.13); $(r = -0.61$, $P = 0.01$, $95\% \text{CI} = -0.71$ to 0.29)], as well as iPMd stimulation [$(r = -0.147$, $P = 0.82$); $(r = -0.0123$, $P = 0.93$)] (Fig. 6A, B). In fact, standard inhibition of cM1 tended to elicit greater improvement in RT performance than iPMd facilitation in patients with mild physiologic damage (MEP_{PRESENT}) ($P = 0.06$). IPMd facilitation offered no such apparent advantage in patients with severe damage (MEP_{ABSENT}) ($P = 0.87$) (Fig. 6C). Overall, results from our main and control experiments show that patients with severe

impairment (based on $UEFM_{PROXIMAL}$) and damage (based on mean FA) show greater improvements in paretic limb RT with cPMd facilitation than with iPMd facilitation, cM1 facilitation or standard inhibition of cM1. Patients with mild impairment and damage however witness more improvement with standard inhibition of cM1.

4. Discussion

This investigation demonstrates for the first time that patients with severe damage and impairment, who show little to no improvement in proximal paretic limb reaching with standard approach to stimulation (involving inhibition of cM1), show improvement with a new approach involving facilitation of cPMd. Control experiments verify improvements witnessed with facilitation of cPMd exceed improvements noted even with facilitation of higher-order ipsilesional (iPMd) and other contralesional motor cortices (cM1). Patients with mild damage and deficit on the other hand show greater improvement with the standard approach. Logistic regression is able to help derive cut-off values of damage and impairment that separate responders to the standard approach from responders to cPMd facilitation (mean FA = 0.5 and $UEFM_{PROXIMAL}$ = 26–28). Responders to the standard approach show improvements in association with increases in output of ipsilesional pathways, whereas responders to cPMd facilitation show improvements in association with reduction in interhemispheric competition levied on iM1. To the best of our knowledge, this is the first preliminary report to document results of facilitation of cPMd in patients with stroke, and offer cut-off values of damage and impairment to separate responders to standard approach vs. the cPMd facilitation technique. Future studies conducted on a larger scale could help validate preliminary cut-offs derived here, and help select candidates for tailored stimulation that carries the promise of improving function in all ranges of severity.

Our finding that the standard approach improves proximal reaching performance in patients who are minimally affected but not in those who are severely impaired can be understood based on neurophysiology. Standard approaches are based on the premise that facilitating iM1, either directly or indirectly by suppressing the contralesional motor cortices (as done here), would increase physiologic output of ipsilesional corticospinal pathways to aid movement of the paretic upper limb (Carey et al., 2008, Di Lazzaro et al., 2008). However, we have found that only patients with minimal damage to such pathways are able to experience an increase in output (Fig. 5A); patients who sustain severe damage showed no such increases. These findings are similar to those reported by other studies (Levy et al., 2008, Ackerley et al., 2010, Nouri et al., 2011, Levy et al., 2015); limits of stroke-related damage dictate whether patients can experience gains in ipsilesional excitability necessary to achieve improvement in movement of the paretic limb. Therefore, stimulation emphasizing iM1 is not a “one-size-fits-all” approach to affect motor function.

Instead, we have demonstrated here for the first time that stimulation emphasizing cPMd is an effective alternative for patients who fail to improve with standard approaches emphasizing iM1. Our finding aligns with long-standing evidence that patients with severe damage following stroke may rely on plasticity of the surviving contralesional motor cortices (Ward et al., 2003b, Calautti et al., 2007, Riecker et al., 2010). The finding that, compared to other contralesional motor cortices (for example, cM1), cPMd is more

important, also agrees with previous evidence such as that offered by Johansen-Berg et al. and Bestmann et al. (Johansen-Berg et al., 2002, Bestmann et al., 2010). These groups had applied stimulation to inhibit cPMd and other areas during ongoing movement the paretic limb, in a cross-sectional design. Based on the degree of slowness elicited, they concluded that cPMd made the greatest causal contribution to paretic limb function in severely affected patients. Our study adopted somewhat of a reverse methodology to lend support to these original findings. We applied stimulation to facilitate cPMd and other areas in a longitudinal design. Based on the degree of improvement elicited in speed of movement of the paretic limb in severely affected patients, we were able to confirm that cPMd made the greatest contribution to their function.

In addition, we conducted neurophysiologic studies to determine why facilitation of cPMd was superior. Facilitation of cPMd (more than facilitation or standard inhibition of cM1) helped alleviate interhemispheric inhibition imposed on iM1. Alleviation of inhibition was pronounced especially in severely affected patients, and related to the improvement in speed of movement of their paretic limb (Fig. 4A, B). CPMd likely has a stronger influence on interhemispheric interactions compared to cM1 because it shares robust callosal connections with iM1 (Rouiller et al., 1994, Fang et al., 2008). CPMd also projects more substantial ipsilateral uncrossed output to supply proximal muscles involved in reaching (Johansen-Berg et al., 2002, Bradnam et al., 2013). Whether changes in ipsilateral output were associated with functional advantage offered by cPMd remains to be tested in future studies. The finding that facilitating cPMd was also more effective than facilitating iPMd in severely affected patients reflects the limited scope of plasticity available across ipsilesional resources in cases of severe insult. Even though iPMd can assume the role of iM1 when pathways from iM1 are damaged in a typical middle cerebral artery stroke affecting white matter at PLIC (Carey et al., 2002, Ward et al., 2003a, Dancause et al., 2011, Ward, 2011), it is unlikely that pathways from iPMd would be spared when a lesion significantly affects pathways from iM1 (Hedna et al., 2013). This may explain why facilitation of iPMd failed to generate a significant increase in MEPs in the paretic upper limb to contribute to improvement in speed. In cases of severe insult, therefore, facilitation of undamaged cPMd could serve as a more consistent resource to promote function of the paretic upper limb.

What is unique about this report is the preliminary identification of a cut-off level of severity that helps stratify patients for tailored stimulation involving the standard approach and facilitation of cPMd. Several landmark studies have informed our study design that is fundamental to generating such type of evidence. Stinear et al., Burke Quinlan et al. (Stinear et al., 2007, Stinear et al., 2012, Burke Quinlan et al., 2015), and others originally helped stratify patients for tailored rehabilitative therapies based on a “unimodal” or a single-therapy study design. They plotted recovery associated with a single type of therapy (y-axis) against baseline damage/impairment (x-axis) and identified the cut-off where recovery reduced sharply. They concluded that patients experiencing less than the cut-off level of damage/impairment were candidates for the chosen modality of rehabilitative therapy, whereas patients experiencing more damage/impairment would require alternate therapies. However, to develop tailored therapies for patients with less as well as more severe damage/impairment, at least a “bimodal” or a two-therapy approach may be necessary. Di Pino et al (Di Pino et al., 2014) had hypothesized that plasticity in recovery is bimodal; that patients

less affected than a cut-off level (i.e., with high “structural reserve”) rely on iM1, while more affected patients, who lack adequate structural reserve, rely on undamaged contralesional motor cortices for recovery. Here, we adopted a bimodal design to test Di Pino et al.’s bimodal hypothesis. We offered patients two alternate (bimodal) forms of stimulation – standard approach designed to facilitate iM1 and a new approach designed to facilitate cPMd. Based on how improvements elicited with both techniques varied with baseline damage/impairment, our study generated elementary evidence about the existence of a cut-off, demonstrating that patients less affected than the cut-off [$UEFM_{PROXIMAL} > 26$, mean $FA > 0.5$] benefit from the standard approach by experiencing gains in ipsilesional output, whereas patients more affected than the cut-off [$UEFM_{PROXIMAL} < 26$, mean $FA < 0.5$] benefit from cPMd facilitation through alleviation of competition imposed on weak iM1. Future studies that recruit a larger population of stroke patients are required to explore validity of these cut-offs in order to prepare for selection of candidates in studies involving tailored stimulation.

Our study has several other limitations. First, our measurement of RT must be carefully interpreted as RT may contain components of both reaction time and movement time. Future studies that employ RT as a measure to measure motor performance of the paretic arm must differentiate between reaction time and movement time, and address how stimulation of different cortices could contribute to the individual modulation of these times. Second, although significant improvements in RT performance were noted following standard inhibition of cM1 vs. cPMd facilitation, the clinical relevance of RT performance on functional recovery needs to be further addressed. Third, we investigated MEPs from EDC since the muscle is involved in placing the wrist during reaching, but future studies should also consider recording MEPs from proximal muscles, like triceps. Fourth, we adopted a single-blinded design, but blinding investigators as well would be beneficial in future studies. Finally, our cut-offs to tailor stimulation are based on single sessions of stimulation. Single sessions were necessary, however, because their effects wash out quickly and are best paradigms for crossover studies. Use of a crossover study was important to confirm that patients improve with stimulation of the tailored substrate, not another substrate.

5. Conclusions

Mildly affected patients showed improvements in proximal reaching performance with standard inhibition of cM1, while severely affected patients showed improvements with cPMd facilitation, yielding cut-offs to stratify candidates for targeted stimulation of each technique. Responders to standard inhibition of cM1 ($UEFM_{PROXIMAL} > 26$, mean $FA > 0.5$) improved via gains in ipsilesional output, whereas responders to cPMd facilitation improved via alleviation of interhemispheric competition imposed on weak iM1. Our preliminary results for the first time provide evidence for the existence of cut-off levels of damage/impairment that can be used to select candidates for tailored stimulation in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. Mildly affected chronic stroke patients improved upon paretic upper limb reaching with standard inhibitory 1Hz rTMS of contralesional motor cortex.
2. Severely affected patients improved with a new method involving facilitatory 5 Hz rTMS of contralesional dorsal premotor cortex.
3. A preliminary cut-off level of damage/impairment separated responders to each form of stimulation.

Fig. 1. Study design. Abbreviations: RT, reaching time; UEFM, Upper Extremity Fugl-Meyer; TMS, transcranial magnetic stimulation; DTI, diffusion tensor imaging; cM1, contralesional primary motor cortex; cPMd, contralesional dorsal premotor cortex; iPMd, ipsilesional dorsal premotor cortex; iM1, ipsilesional primary motor cortex. *Note:* To facilitate iM1, we used a standard approach that involved inhibition of cM1 using 1Hz rTMS.

Fig. 2.

Outcomes and Neurophysiology. Abbreviations: MEP, motor evoked potential; EMG, electromyography; AMT, active motor threshold; iSP, ipsilateral silent period. **(A)** Outcomes are recorded as time to perform proximal reaching at the paretic upper limb, or reaching time **(B)** Neurophysiology is studied as changes in corticospinal output and interhemispheric inhibition imposed on iM1 from contralesional motor cortices. Corticospinal output is computed as percent change in amplitude of (normalized) MEPs from pre- to post-rTMS, while patients maintained 20%–50% maximum volitional contraction of the contralateral (paretic) target muscle (top panel). Interhemispheric inhibition is calculated as percent change in iSP relative to mean prestimulus EMG from pre- to post-rTMS, while patients maintained 50% maximum volitional contraction of the ipsilateral (paretic) target muscle (bottom panel).

Fig. 3.

Main experiment — Outcomes. Abbreviations: RT, reaching time; MEP, motor evoked potential; cPMd, contralesional dorsal premotor cortex; FA, fractional anisotropy; UEFM, Upper Extremity Fugl-Meyer. Change in RT performance (ms or %) vs (A) Baseline impairment (UEFM_{PROXIMAL}), (B) Baseline damage (mean FA) and (C) Baseline damage (presence or absence of MEP) with standard approach and cPMd facilitation. At severe UEFM_{PROXIMAL} and mean FA values, standard approach elicited little to no improvement in RT performance, whereas cPMd facilitation elicited significant improvement. Cut-off values of UEFM_{PROXIMAL} and mean FA (23 and 0.46 respectively) are indicated by an 'x'. Although patients with severe physiologic damage (MEP_{ABSENT}) seemed to respond more to cPMd facilitation, and patients with less damage (MEP_{PRESENT}) to standard approach, findings were not significant. (D) Decision tree stratifying responders for standard approach vs cPMd facilitation technique.

Fig 4.

Sub-experiment. Abbreviations: RT, reaching time; iSP, ipsilateral silent period; cM1, contralesional primary motor cortex; cPMd, contralesional dorsal premotor cortex. **(A)** cPMd but not cM1 facilitation tended to show more improvements in RT performance in severely affected patients, and tended to show greater reduction in iSP **(B)**.

Fig. 5.

Main experiment — Neurophysiology. Abbreviations: MEP, motor evoked potential; RT, reaching time; iSP, ipsilateral silent period; cPMd, contralesional dorsal premotor cortex; AMT, active motor threshold; UEFM, Upper Extremity Fugl-Meyer. **(A)** Percent change in MEP vs Baseline damage (AMT) with standard approach. Patients with mild physiologic damage (lower AMT) showed notable increases in paretic MEPs. Paretic MEPs are shown for a patient with lower AMT and for a patient with higher AMT at pre- and post-stimulation. **(B)** Percent change in MEP vs change in RT performance (ms) with standard approach. Increase in paretic MEPs were associated with improvements in RT performance. **(C)** Percent change in iSP vs Baseline impairment (UEFM_{PROXIMAL}) following cPMd facilitation. Severely impaired patients (lower UEFM_{PROXIMAL}) showed greater reduction in iSP. Average iSPs are shown for a mildly impaired patient and a severely impaired patient at pre- and post-stimulation. **(D)** Percent change in iSP vs change in RT performance following cPMd facilitation (ms). Reduction in iSPs were associated with improvements in RT performance. *Note:* Patient 1 (UEFM_{PROXIMAL} = 7) showed substantial reduction in iSPs. When we repeated the analysis without this individual, reduction in iSPs were still associated with improvements in RT performance.

Fig. 6.

Control experiment. Abbreviations: RT, reaching time; MEP, motor evoked potential; iPMd, ipsilesional dorsal premotor cortex; cM1, contralesional primary motor cortex; cPMd, contralesional dorsal premotor cortex; FA, fractional anisotropy; UEFM, Upper Extremity Fugl-Meyer. Change in RT performance (ms or %) vs (A) Baseline impairment (UEFM_{PROXIMAL}), (B) Baseline damage (mean FA) and (C) Baseline damage (presence or absence of MEP) with standard approach and cPMd facilitation. At severe UEFM_{PROXIMAL} and mean FA values, both standard approach and iPMd facilitation elicited little to no improvement in RT performance. Improvements in RT performance with iPMd facilitation were smaller than improvements in RT performance with standard approach in patients with less physiologic damage (MEP_{PRESENT}), and were not any better in patients with more damage (MEP_{ABSENT}).

Table 1

(A) Clinico-demographic information.

ID	Age/Gender/Handedness	Time since stroke (months)	Side of Paresis	MMSE	Lesion volume (cm ³)	Lesion location	Stroke Subtype	Mean FA	MEP	UEFM _{TOT} AL/UEFM _{PRO} XIMAL (max = 66/36)	Baseline predictors	Baseline values (mean ± SEM)	Correlation with change in RT performance associated with standard approach /cPmd facilitation
1	56/F/R	24	L	29	245.8	Cortical & subcortical	Ischemic	0.268	–	7/7	<u>Demographics</u>		
2	58/M/R	264	L	29	199.2	Cortical & subcortical	Ischemic	0.290	–	21/12	Age (years) [range]	62.13 ± 2.33	0.29/–0.09
3	76/M/R	24	R	28	0.9	Subcortical	Ischemic	0.493	+	24/11	Gender (M/F)	13M/2F	–0.33/–0.32
4	55/M/R	45	R	30	1.4	Subcortical	Ischemic	0.415	–	25/13	Handedness (L/R)	0L/15R	NA
5	55/M/R	48	R	27	1.2	Subcortical	Ischemic	0.347	–	32/18	Time since Stroke (months) [range]	55.6 ± 15.69	–0.32/–0.09
6	77/M/R	84	R	30	1.0	Subcortical	Ischemic	0.325	+	42/21	Side of Paresis (L/R)	6L/9R	–0.13/–0.003
7	69/M/R	48	R	30	1.2	Subcortical	Hemorrhagic	0.515	–	44/27	<u>Cognitive/mood</u>		
8	53/M/R	34	R	29	NA	Subcortical	Ischemic	NA	–	46/27	MMSE	28.6 ± 0.51	–0.36/0.01
9	66/M/R	19	L	24	9.4	Cortical	Ischemic	0.53	+	48/25	<u>Lesion</u>		
10	54/M/R	29	R	29	2.4	Subcortical	Ischemic	90.398	+	52/28	Lesion location (cortical/subcortical/cortical & subcortical/pontine)	(1/12/2/2)	0.25/–0.43
11	51/F/R	23	R	29	0.6	Subcortical	Ischemic	0.492	+	52/29	Lesion volume (cm ³)	33.14 ± 20.1	–0.42/0.48
12	56/M/R	13	L	28	0.3	Subcortical	Ischemic	0.564	+	60/33	<u>Impairment</u>		
13	63/M/R	45	L	28	0.5	Pontine	Ischemic	0.552	+	61/35	UEFM _{TOTAL} [range]	42.53 ± 4.43 [7–63]	–0.42/0.81*
14	62/M/R	11	R	30	0.1	Subcortical	Ischemic	0.555	+	61/33	uefm_{PROXIMAL} [range]	23.67 ± 2.44 [7–36]	–0.62*/0.90*
15	72/M/R	84	L	26	0.01	Pontine	Ischemic	0.577	+	63/36	UEFM _{HAND} [range]	18.87 ± 2.06 [0–28]	–0.40/0.79*
											<u>Damage</u>		
											MEP (+/–)	9+/6–	–0.49*/0.46#
											Mean FA	0.42 ± 0.04	–0.61*/0.72*

Abbreviations: MMSE, Mini Mental State Examination; FA, fractional anisotropy; MEP, motor evoked potential; UEFM, Upper Limb Fugl-Meyer. *Note:* ID=Patient; order of patients is in ascending order of their UEFM_{TOTAL} score; “+,” represents “MEPPRESENT” and “–” represents “MEPABSENT”. (B) Distribution of baseline predictors and correlation with change in RT performance associated with standard approach and cPmd facilitation. Highlighted in bold are baseline predictors that showed significant relationship (P < 0.05, marked as *) or trend towards significance (P < 0.08, marked as #) with change in RT performance associated with standard approach (inhibition of cPmd. *Note:* UEFM_{TOTAL} and UEFM_{HAND} showed significant relationship with change in RT performance associated with cPmd facilitation but not with the standard approach. Since our goal was to identify what level of damage/impairment separated responders for standard approach vs. cPmd facilitation, we included only those predictors which showed significant correlation with change in RT performance associated with both techniques.