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Stratifying chronic stroke patients based on the influence of contralesional motor cortices: an inter-hemispheric inhibition study

Yin-Liang Lin^{1,2}, Kelsey A. Potter-Baker^{1,3,12}, David A. Cunningham^{1,4,5,6}, Manshi Li⁷, Vishwanath Sankarasubramanian^{1,8}, John Lee⁹, Stephen Jones¹⁰, Ken Sakaie¹⁰, Xiaofeng Wang⁷, Andre G. Machado¹¹, Ela B. Plow^{1,9}

¹Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

²Department of Physical Therapy and Assistive Technology, National Yang-Ming University, Taipei, Taiwan

³Advanced Platform Technology Center, Louis Stokes Cleveland Department of Veteran's Affairs, Cleveland, OH, USA

⁴Department of Physical Medicine and Rehabilitation, Case Western Reserve University, Cleveland, OH, USA

⁵MetroHealth Rehabilitation Institute of Ohio, MetroHealth Medical Center, Cleveland, OH, USA

⁶Cleveland Functional Electrical Stimulation Center, Louis Stokes Cleveland Department of Veteran's Affairs, Cleveland, OH, USA

⁷Respiratory Institute Biostatistics Core, Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

⁸Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

⁹Department of Physical Medicine and Rehabilitation, Neurological Institute, Cleveland Clinic, OH, USA

¹⁰Department of Diagnostic Radiology, Imaging Institute, Cleveland Clinic, Cleveland, OH, USA

¹¹Neurological Institute, Cleveland Clinic, OH, USA

¹²Department of Health and Biomedical Sciences, University of Texas Rio Grande Valley, Edinburg, TX, USA

Corresponding author: Ela B. Plow, PhD, PT, Department of Biomedical Engineering/ND20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA, Phone: +1-216-445-4589, Fax: +1-216-444-9198, plowe2@ccf.org.

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Conflict of Interest

Andre G. Machado has the following conflicts of interest: ATI, Enspire and Cardionomics (distribution rights from intellectual property), St Jude (consultant) and Medtronic (Fellowship support). Other authors declare that there is no conflict of interest associated with this work. Specifically, there are no financial or personal relationships with other people or organizations that could inappropriately influence or bias this work.

Abstract

Objective: A recent “bimodal-balance recovery” model suggests that contralesional influence varies based on the amount of ipsilesional reserve: inhibitory when there is a large reserve, but supportive when there is a low reserve. Here, we investigated the relationships between contralesional influence (inter-hemispheric inhibition, IHI) and ipsilesional reserve (corticospinal damage/impairment), and also defined a criterion separating subgroups based on the relationships.

Methods: Twenty-four patients underwent assessment of IHI using Transcranial Magnetic Stimulation (ipsilateral silent period method), motor impairment using Upper Extremity Fugl-Meyer (UEFM), and corticospinal damage using Diffusion Tensor Imaging and active motor threshold. Assessments of UEFM and IHI were repeated after 5 week-rehabilitation (n=21).

Results: Relationship between IHI and baseline UEFM was quadratic with criterion at UEFM 43 (95% confidence interval: 40-46). Patients less impaired than UEFM=43 showed stronger IHI with more impairment, whereas patients more impaired than UEFM=43 showed lower IHI with more impairment. Of those made clinically-meaningful functional gains in rehabilitation (n=14), more-impaired patients showed further IHI reduction.

Conclusions: A criterion impairment-level can be derived to stratify patient-subgroups based on the bimodal influence of contralesional cortex. Contralesional influence also evolves differently across subgroups following rehabilitation.

Significance: The criterion may be used to stratify patients to design targeted, precision treatments.

Keywords

Stroke; Inter-hemispheric Inhibition (IHI); Transcranial Magnetic Stimulation (TMS); Corticospinal; Diffusion Tensor Imaging (DTI); Upper Limb; Motor Function; Rehabilitation

1. Introduction

After stroke, the influence of contralesional motor cortices on motor function of the paretic upper limb remains widely debated. Classical evidence has suggested that contralesional influence is negative, that contralesional motor cortices impose excessive inter-hemispheric inhibition (IHI) and further limit motor output to the paretic upper limb (Duque et al., 2005, Murase et al., 2004). However, more recent evidence has indicated the influence is positive, that contralesional motor cortices can make supportive contributions towards paretic limb movement especially in patients who lack adequate ipsilesional resource (Bestmann et al., 2010, Johansen-Berg et al., 2002, Lotze et al., 2006, Mohapatra et al., 2016, Sankarasubramanian et al., 2017). A recent model known as the “bimodal-balance recovery hypothesis” has attempted to reconcile evidence, postulating that the role of contralesional motor cortices may vary based on the amount of ipsilesional reserve and neural pathways available to contribute to recovery (Di Pino et al., 2014). When the ipsilesional reserve is high (i.e., when there is limited damage), contralesional influence is believed to be inhibitory, whereas when the ipsilesional reserve is low (i.e., when there is more severe damage), the contralesional influence is thought to be supportive for paretic limb motor function (Di Pino et al., 2014).

However, direct evidence of a bimodal role of contralesional motor cortices is lacking. If patients indeed experience different types of contralesional influence, a threshold or criterion-level of reserve should be possible to identify to separate patients. Knowledge of such a criterion can help design individualized patient treatments, such as neuromodulation targeting the contralesional hemisphere based on its influence on paretic-limb movement (Plow et al., 2009). Therefore, the primary objective of the present study was to investigate the relationship between contralesional influence and ipsilesional reserve in patients with chronic stroke and identify a criterion level of reserve that separates patient-subgroups showing differing relationships. We further sought to confirm the identified criterion by determining whether contralesional influence indeed evolves differently in the stratified subgroups following a course of rehabilitation.

Patients with chronic stroke with wide-ranging spectrum of impairment severity (mild to severe) were studied. We defined contralesional influence as interhemispheric inhibition (IHI) collected using Transcranial Magnetic Stimulation (TMS). We expressed “reserve” in the context of structural integrity and neurophysiologic potentials of residual corticospinal pathways, tested using Diffusion Tensor Imaging (DTI) and TMS respectively. We used Upper Extremity Fugl-Meyer (UEFM) scale to assess motor impairment. First, we characterized the relationship between IHI imposed from contralesional motor cortex and baseline impairment and reserve. Based on the relationship, we identified criterion levels of impairment and reserve that separated “less-affected” and “more-affected” patient-subgroups. Finally, to determine whether IHI modulates differently across identified subgroups, we compared the change in IHI observed over the course of motor functional improvements achieved with rehabilitation. In line with the original bimodal-balance recovery hypothesis, we anticipated that contralesional motor cortices would impose higher IHI in less-affected and reduced IHI in more-affected patients. In addition, we expected that a criterion severity level would separate subgroups differing on the basis of relationship with IHI and that the criterion would be confirmed by longitudinal findings of further reduction in IHI following rehabilitation in more-affected patients.

Even though our goal was to find direct evidence in line with the bimodal-balance recovery model, there were differences between the assumption of the present work and the original model. Bimodal balance recovery model was proposed to predict motor recovery achieved in the chronic phase based on two variables acquired in the acute phase – “reserve” and contralesional influence (IHI) (Di Pino et al., 2014). We extended this model for use in the chronic phase. We made the assumption that in the chronic phase, ipsilesional reserve had contributed to motor function recovery and some recovery have been made (measured as impairment). This indicates that the relationship between reserve and impairment has likely reached a static function in the chronic phase. As such, we adopt the flexibility of treating “impairment” as an index of “reserve” to study its relationship with IHI. Despite differences and assumptions, our present work seeks to build upon the original bimodal-balance recovery model by identifying criterion level of severity to separate patients with distinct contralesional influences and validating the criterion through longitudinal study to help stratify patients for targeted therapies in future.

2. Methods

2.1 Subjects and design

Patients with unilateral upper limb paresis following a first-ever, ischemic or hemorrhagic stroke (chronic, ≥ 6 months ago) were included (Table 1). Patients were between the ages of 21 and 80 years and possessed at least trace movement of paretic thumb or fingers. Patients with severe cognitive impairment (Mini-Mental State Examination score < 24 out of 30), cerebellar stroke, contraindication to TMS (Rossi et al., 2009) and /or history of intake of neuro- or psycho-active medications were excluded. Patients that had received Botox or occupational therapy within 3 months prior to or after enrollment were also excluded. A sample of right-handed, age-matched healthy control subjects without neurological or musculoskeletal impairment was also studied. The purpose of including aged healthy controls was to derive age-based norms of neurophysiology and imaging for comparison with patients with chronic stroke. The Institutional Review Board of the Cleveland Clinic approved the study and written informed consent was obtained from all participants.

Twenty-four patients (mean ± standard deviation, 61.7 ± 8.9 years) and 11 healthy control subjects (63.8 ± 11.7 years) were enrolled. Patients underwent motor impairment (UEFM), DTI and TMS assessments at baseline. UEFM and TMS assessments were repeated after 5 weeks of upper limb rehabilitation (details follow). Healthy control subjects only completed baseline DTI and TMS assessments. Analysis at baseline included results from all patients and healthy controls. But baseline-to-posttest analysis was only performed for patients that had “response” to rehabilitation, defined as the attainment of minimal clinically important difference (MCID) or ≥ 4.25-point UEFM gain (Page et al., 2012).

Patients that underwent rehabilitation received it as part of a clinical trial investigating the effects of adjunctive transcranial direct current stimulation (tDCS). Whether a patient received tDCS or sham with rehabilitation is denoted in Table 1. Addition of tDCS to rehabilitation did not produce significantly greater motor improvement (UEFM) or change in neurophysiology (corticospinal excitability and IHI) (Supplementary Table 1). Therefore, data from both tDCS + rehabilitation and sham + rehabilitation groups has been combined for purposes of this study. To ensure no bias, effect of original group assignment has been controlled for in the current analyses (see statistical analysis section below).

2.2 Motor Impairment (UEFM)

UEFM score was collected at baseline and at post-training after 5 weeks of rehabilitation. UEFM is a reliable and valid measure of post-stroke upper limb motor impairment (Berglund and Fugl-Meyer, 1986, Duncan et al., 1983, Fugl-Meyer et al., 1975, Platz et al., 2005, Sanford et al., 1993). The UEFM items take into account synergy patterns, isolated movement, coordination, and reflex activity based on the motor recovery concept of Twitchell and Brunnstrom (Fugl-Meyer et al., 1975). Volitional movement of the upper limb (shoulder, elbow, forearm, wrist, and hand) is examined. Each item is graded on a 3-point ordinal scale (0, cannot perform; 1, perform partially; and 2, perform fully) and summed to provide a maximum score of 66. Since movements of both the proximal and distal upper

limb are assessed, UEFM is suitable for characterizing impairment across the entire mild-to-severe spectrum.

2.3 Lesion characteristics and corticospinal damage (MRI and DTI)

At baseline, subjects underwent MRI that included T1-MPRAGE acquisition and high angular resolution diffusion-weighted imaging (HARDI) acquisition performed on Siemens 3T TIM Trio (17 patients, 8 healthy subjects) or Prisma scanner (7 patients, 3 healthy subjects) (Siemens Healthcare GmbH, Erlangen, Germany). T1-MPRAGE data included one hundred seventy-six, 1-mm thick axial slices with a field-of-view of 256 mm x 256 mm, TE = 1900ms, TR = 1.71ms, flip angle = 8°. On T1-weighted images, lesion locations were identified with guidance from co-author neurosurgeon (AM). Lesion volume was characterized using MRIcro (from Prof. Christopher Rorden, University of South Carolina; <http://www.mccauslandcenter.sc.edu/mricro/>) (Zhu et al., 2010).

HARDI data included 71 diffusion-weighting gradients ($b = 1000 \text{ s/mm}^2$) and 8 T2-weighted image volumes ($b = 0 \text{ s/mm}^2$) acquired at 2mm isotropic resolution. Data was preprocessed to correct for eddy current distortion and head motion (Sakaie and Lowe, 2010). A unit-less measure of tissue integrity, known as fractional anisotropy (FA), which is based on the estimation of magnitude and directionality of water diffusion, was calculated (Jones et al., 2013, Lindenberg et al., 2010, Stinear et al., 2007, Sundgren et al., 2004, Zhu et al., 2010). A threshold value of FA = 0.2 was used to visualize the FA map (Cunningham et al., 2015a, Lowe et al., 2008, Potter-Baker et al., 2016, Sakaie and Lowe, 2007, Zhang et al., 2013). FA was measured at the level of posterior limb of the internal capsule (PLIC), a major convergence point for corticospinal tracts (Cunningham et al., 2015a, Plow et al., 2013). Characterization of FA at the level of PLIC is a common and widely-accepted approach across stroke laboratories (Lindenberg et al., 2010, Stinear et al., 2007) because it is sensitive to capturing the effect of the insult given that upper extremity motor deficits commonly arise from lesions involving the PLIC or nearby structures. In addition, FA values at PLIC are predictive of motor impairment, and functional gains (Lindenberg et al., 2010, Stinear et al., 2007). PLIC was defined on three consecutive slices centered at the foramen of Monroe in axial FA plane (b_0 space) (Puig et al., 2011, Sidaros et al., 2008). FA for ipsilesional PLIC was expressed relative to the FA for contralesional PLIC using $FA_{\text{Asymmetry}}$ (equation 1). Values of $FA_{\text{Asymmetry}}$ range between -1 and +1, where higher values indicate substantial loss of ipsilesional corticospinal pathways (poor ipsilesional reserve).

$$FA_{\text{Asymmetry}} = \frac{FA_{\text{contralesional}} - FA_{\text{ipsilesional}}}{FA_{\text{contralesional}} + FA_{\text{ipsilesional}}} \quad (1)$$

2.4 IHI and residual pathway excitability (TMS)

TMS assessments were performed at baseline and post-training after 5-weeks to characterize IHI and excitability of residual pathways. TMS was delivered to motor cortices using a 70-mm figure-of-eight coil. The coil was positioned at a 45° angle to midline with its handle oriented backward and laterally (Magstim200², Magstim Co. Ltd., Whitland, UK).

Frameless stereotaxy was used to guide the application of TMS (Brainsight, Rogue Research, Montreal, QC, Canada). Subject's cranial landmarks were registered to the model generated based on their T1-weighted MRI. This anatomic MRI was used as a guide to identify a general region in which to localize motor cortices. The stereotactic software conveyed real-time information about the TMS coil and its relation to subject's brain anatomy. This procedure affords precision, accuracy and consistency in TMS targeting (Cunningham et al., 2015a). Electromyographic (EMG) signals were collected from the first dorsal interosseous (FDI) muscle using surface electrodes. FDI muscle was chosen because of its relevance for performance of fine motor tasks impaired commonly after stroke. Ag-AgCl (8-mm diameter) electrodes were placed in a belly-belly montage. EMG signals were sampled at 2KHz, amplified at gain of 500, filtered (10 Hz–2KHz) and stored for offline analysis (PowerLab 4/25T, ADInstruments Inc., Colorado Springs, CO).

With guidance from frameless stereotaxy, TMS motor hotspots were identified for the left and the right FDI muscles in the motor regions identified using subject's anatomic MRI. Motor hotspot was defined as the site eliciting contralateral motor evoked potentials (MEPs) at the lowest TMS intensity. The lowest intensities used to trigger responses are referred to as thresholds (expressed as %Maximum Stimulator Output or %MSO). Resting motor threshold (RMT) and active motor threshold (AMT) were tested in this study. RMT is the lowest intensity required to generate 50 μ V MEPs in resting state, while AMT is the lowest intensity required to generate 200 μ V MEPs in slightly contracted state (20% of maximum voluntary contraction force, MVC) in 50% of trials [10 trials collected based on International Federation of Clinical Neurophysiology (IFCN) guidelines] (Groppa et al., 2012, Rossini et al., 1994). A higher amplitude cut-off was chosen for AMT than RMT to avoid misclassifying background EMG signals as MEPs (Groppa et al., 2012, Rossini et al., 1994). Both RMT and AMT serve as indicators of pathway excitability, but AMT carries specific advantage because it can be acquired even in individuals who do not have resting MEPs due to severe damage (Stinear et al., 2007). Contralesional RMT in patients and RMT of left hemisphere in healthy controls were acquired to scale intensities needed for IHI testing, per published methodology (Cunningham et al., 2015b, Harris-Love et al., 2011).

IHI from the contralesional to the ipsilesional hemisphere in patients and from the dominant (left) to the non-dominant hemisphere (right) in healthy subjects was tested. IHI was collected using the ipsilateral silent period (iSP) method (we therefore called IHI assessed with the iSP method IHI-iSP). The iSP method involves applying supra-threshold TMS to the hemisphere ipsilateral to the contracting (test) muscle; TMS produces transient suppression ('silence') of the ongoing EMG activity in the contracting muscle (Figure 1). ISP is believed to reflect IHI imposed from the targeted ipsilateral motor cortex upon the contralateral motor cortex controlling the (active) contracting limb. IHI is believed to be mediated via transcallosal projections and their terminations on intra-cortical circuits within each hemisphere (Chen et al., 2003).

We chose to test IHI using the iSP method because of the specific advantage it offers over the traditional bi-hemispheric method used for assessment of IHI. Using the bi-hemispheric method, TMS is given to both hemispheres at slightly offset latencies and IHI is defined as the suppression of contralateral MEPs produced by preceding (conditioned) TMS pulses

given to the ipsilateral motor regions (Chen et al., 2003, Ferbert et al., 1992). Bi-hemispheric TMS method is contingent upon the presence of MEPs, which are many times impossible to elicit in severe patients. Therefore, the iSP method is a suitable alternative to record IHI in more impaired individuals (Bradnam et al., 2012, Harris-Love et al., 2011, Sankarasubramanian et al., 2017).

ISP was elicited during the isometric contraction (50% MVC) of paretic FDI in patients and during the isometric contraction of non-dominant (left) FDI in healthy subjects. Supra-threshold TMS pulses (150% RMT, n=20) were given to the motor hotspot in the ipsilateral hemisphere. TMS produced contralateral MEPs and after a short delay generated transient suppression of ongoing ipsilateral EMG ("silence" or iSP). Onset of iSP was defined as the time-point at which rectified EMG fell below 1 standard deviation (SD) of pre-stimulus voluntary EMG for at least five data points, and offset of iSP was defined as the time-point at which EMG returned through this level (Figure 1)(Chen et al., 2003, Cunningham et al., 2015a, Cunningham et al., 2015b). IHI-iSP was calculated as % decrease in EMG amplitude seen during iSP expressed relative to pre-stimulus EMG amplitude (averaged over 85 ms), a common calculation used to derive IHI on the basis of iSP (equation 2) (Cunningham et al., 2015b, Perez et al., 2014).

$$IHI - iSP = \frac{Mean_{pre-stimulus} - Mean_{iSP}}{Mean_{pre-stimulus}} \times 100 \% \quad (2)$$

Certain methodological factors may influence the levels of IHI-iSP, for example ipsilateral MEPs elicited in the contracting test muscle, amplitude of background contraction of the muscle, and intensity of supra-threshold TMS pulse applied to the ipsilateral hemisphere. Safeguards were adopted to ensure these methodological factors do not confound the measurement of IHI-iSP. If an ipsilateral MEP were detected, the trial was excluded from analysis. To ensure that amplitude of background contraction was not variable, subjects were given real-time view of their EMG activity and the target level (50% MVC) to be maintained throughout the experiment. Subjects (especially stroke patients) were also given adequate rest breaks to minimize the effects of fatigue on background muscle activity. In addition, statistical analyses were performed to ensure that amplitude of background EMG and TMS intensity used did not confound the observed IHI-iSP results (see Results).

2.5 Task-oriented rehabilitation for participants with stroke

Within a week of completion of baseline testing, rehabilitation training was initiated for the paretic upper limb among patients. Rehabilitation protocol was based on task-oriented principles (Wolf et al., 2005). Tasks were developed in line with patient-specific goals and interests. A graded, regimented, feedback-driven approach was used with guidance from a physical therapist (EP). Patients received training for 30 minutes, twice a day, 3 days a week for 5 weeks (details in Cunningham et al. 2015b and Plow et al., 2013). Post-training assessments were performed within a week of completion of rehabilitation training. These assessments included repeat measurement of UEFM and TMS.

2.6 Statistical analysis

We first characterized the relationships between baseline IHI-iSP and baseline impairment (UEFM) and corticospinal damage ($FA_{\text{Asymmetry}}$ and AMT). We determined whether the relationship was linear or quadratic, based on a likelihood ratio test that assesses the difference in goodness of fit between linear and quadratic models. A non-significant result ($p \geq 0.05$) indicated the relationship was linear. A significant result ($p < 0.05$) meant there was a significant difference between the goodness of fit offered by both models, in which case values of R^2 and Akaike information criterion (AIC) were used to decide whether a linear or a quadratic model provided better fit. If a quadratic model provided a better fit (higher R^2 and lower AIC), then the relationship was deemed quadratic, otherwise linear.

Once the type of relationship between IHI-iSP and baseline severity metrics was determined, criterion levels of impairment (UEFM) and damage ($FA_{\text{Asymmetry}}$ and AMT) that separated patients into subgroups were identified. For variables that shared a linear relationship with IHI-iSP, the criterion was identified using a logistic regression model and a receiver-operating characteristic (ROC) curve. Area under the ROC curve was used to determine how well the criterion value separated patients into different severity subgroups: less-affected and more-affected. The criterion value yielding the largest area under the ROC curve was chosen. Odds ratio was also calculated. For variables sharing a quadratic relationship with IHI-iSP, a segmented-type change point of threshold regression model was used to identify the criterion (Julious, 2001). Essentially, the relationship was fit with a two-line regression model, where the slope of the regression suddenly changes at a point without any discontinuity in the relationship. The point at which the slope changes was identified as the criterion (Julious, 2001). α level for all regression analyses was set at 0.05.

Once the criterion level was identified, we compared rehabilitation-associated changes in IHI-iSP in patient subgroups (less affected vs. more-affected). Only responders, who achieved more than 4.25-point UEFM gain (MCID) after rehabilitation, were included in this analysis (Page et al., 2012). An independent-samples *t*-test was used to check for baseline differences in IHI-iSP. Post-training IHI-iSP was compared using a one-way ANCOVA with original group assignment “tDCS or sham” included as covariate. Relationships between change in IHI-iSP and change in UEFM were also studied using Pearson’s (*r*) correlation, α level was again set at 0.05.

3. Results

Twenty-four patients and 11 healthy control subjects participated in the study (Table 1). Clinicodemographic characteristics, lesion, and baseline UEFM, AMT, $FA_{\text{Asymmetry}}$ and IHI-iSP values are presented in Table 1. Patients had experienced mild to severe upper limb motor impairment (UEFM: 15 – 65) and corticospinal damage ($FA_{\text{Asymmetry}}$: -0.021 – 0.590). Corticospinal damage could not be assessed in one patient due to claustrophobia. Ipsilesional AMT values ranged between 30% and 100% MSO across patients. MEPs could not be elicited in 4 patients (UEFM= 19, 22, 29, 42). IHI-iSP ranged between 60.6% and 80.6% across patients and could not be acquired in one patient. Average TMS intensity used to acquire IHI-iSP was $69.2 \pm 13\%$ MSO in patients. Average onset of iSP was at 32.0 ± 5.3 ms after TMS artifact and background EMG activity maintained during iSP testing was

39.0 ± 24.9% MVC. Compared to healthy control subjects, the AMT and FA_{Asymmetry} in patients are significantly higher ($p < 0.05$, Table 1). But there was no significant difference in IHI-iSP between patients and healthy subjects ($p > 0.05$, Table 1). Twenty-one patients successfully completed rehabilitation training, and both baseline and post-training assessments; fourteen of them qualified as responders, who achieved clinically meaningful gains on UEFM (4.25 points).

3.1 Characterizing the relationship between IHI-iSP and severity metrics and identifying the criterion level of severity

The relationship between baseline IHI-iSP and impairment (UEFM) was quadratic (Table 2, Figure 2A). The threshold regression model was significant and the criterion UEFM level could be identified at 43 (95% confidence interval: 40 to 46) (equation 3). Results of threshold regression model showed that among patients that were more affected than UEFM 43, the relationship (slope) between IHI-iSP and baseline UEFM was positive, i.e., IHI-iSP was weaker with lower UEFM (more severe impairment), while among patients that were less affected than UEFM 43 the relationship was negative, i.e., IHI-iSP was stronger with lower UEFM (more severe impairment) (equation 3, Figure 2A)

$$\text{IHI-iSP} = \begin{cases} 50.21 + 0.58\text{UEFM}, & \text{if } \text{UEFM} \leq 43, p = 0.021; \\ 105.12 - 0.7\text{UEFM}, & \text{if } \text{UEFM} > 43, p < 0.0001 \end{cases} \quad (3)$$

Baseline IHI-iSP also had quadratic relationships with AMT and FA_{Asymmetry} (Figure 2B, 2C). Criterion of AMT and FA_{Asymmetry} could be identified at 65% MSO (95% confidence interval: 34% to 96% MSO) and 0.22 (95% confidence interval: -0.13 to 0.56), respectively. However, models for both were non-significant (AMT < 65%, Slope: 0.15, $p = 0.893$ and AMT > 65%, Slope: -0.803, $p = 0.435$; FA_{Asymmetry} < 0.22, Slope: 40.78, $p = 0.969$ and FA_{Asymmetry} > 0.22, Slope: -93.52, $p = 0.932$). Therefore, criterion levels of severity could not be identified based on corticospinal damage and excitability; only impairment severity (UEFM) could separate patient-subgroups showing different relationships with contralesional influence.

To test whether confounding factors had any effect on observed relationships, we evaluated whether IHI-iSP had a relationship with TMS intensity used to target the contralesional hemisphere, or level of paretic FDI contraction maintained. We found IHI-iSP had no significant relationships with intensity of TMS used or the level of paretic FDI contraction maintained ($p = 0.654$ and $p = 0.727$, respectively). Therefore, relationships seen between baseline IHI-iSP and impairment severity could not be explained based on methodological confounds.

3.2 Comparing IHI-iSP modulation over the course of functional improvements seen in less-affected vs. more-affected patients

Of the 14 patients who achieved clinically meaningful improvements on UEFM, six could be categorized as less-affected and eight could be labeled as more-affected based on the criterion of UEFM 43. There was no difference in IHI-iSP between these subgroups at baseline ($t(10.43) = -1.01$, $p = 0.337$). However, at post-training, IHI-iSP in the more-

affected subgroup was significantly lower ($F(1, 11) = 406.82, p = 0.012$; Figure 3A) and it was even lower than that in aged healthy control participants (Figure 3A). Therefore, more-affected patients showed a greater reduction in IHI-iSP following rehabilitation training. Reduced IHI-iSP in the more-affected subgroup at post-training could not be explained based on methodological confounds because TMS intensities delivered to contralesional motor cortices and level of paretic FDI contraction sustained during IHI-iSP testing did not differ between patient-subgroups at post-training ($p = 0.198$ and $p = 0.134$, respectively).

Training-associated change in IHI-iSP was related to UEFM gain but only in the less-affected subgroup. Less-affected patients who showed greater reduction in IHI-iSP also made greater gains on UEFM ($r = -0.92, p = 0.009$; Figure 3D). Even though most patients in the more-affected subgroup showed reduction in IHI-iSP, their change in IHI-iSP was not related to the gains they made on UEFM ($r = -0.002, p = 0.996$; Figure 3C).

4. Discussion

The goals of this study were to characterize the relationship between contralesional influence (defined using IHI-iSP) and baseline severity of damage and motor impairment in chronic stroke, and identify criterion levels of severity that separate patient-subgroups based on the relationships of IHI-iSP. Further, we sought to confirm the identified criterion in a *longitudinal* investigation by demonstrating that IHI-iSP indeed evolves differently in recovery across severity subgroups. Our findings reveal that IHI-iSP shares a non-linear/quadratic or ‘*bimodal*’ relationship with severity of baseline impairment (UEFM). A criterion can be identified at UEFM 43. Patients less impaired than UEFM 43 (less-affected subgroup) show stronger IHI-iSP with more severe impairment, whereas patients more impaired than UEFM 43 (more-affected subgroup) show weaker IHI-iSP with more severe impairment (Figure 2A). These findings match the concepts of the recent bimodal-balance recovery hypothesis, which postulates that contralesional influence varies in a bimodal manner across different levels of ipsilesional reserve. Criterion identified here was further validated in a longitudinal investigation showing that IHI indeed modulates differently with motor improvements across the less-affected versus the more-affected patients, with the more-affected subgroup showing further reduction in IHI-iSP over the course of rehabilitation. Even among less-affected individuals, those showing greater reduction in IHI-iSP achieve greater motor improvements. Overall, therefore, IHI-iSP reduction is a functionally relevant mechanism. Criterion identified here based on contralesional influence may be suitable for stratifying patients for design of precise and effective treatments.

Our finding of a non-linear/quadratic relationship between baseline IHI-iSP and UEFM has important implications. First, it explains why IHI-iSP in stroke is not different from that in healthy controls. Our study has found that levels of IHI-iSP vary parabolically with motor impairment. While some subjects experience stronger IHI-iSP, others show reduced IHI-iSP. This type of distribution lends to no difference in baseline IHI-iSP between patients and healthy controls, which is similar to the findings of a recent meta-analysis (McDonnell and Stinear, 2017). Second, and on a more important note, a parabolic relationship observed between IHI-iSP and baseline UEFM explains why evidence regarding the role of contralesional motor cortices has been divided. Our study has found IHI-iSP to be stronger

with lower UEFM among patients in the less-affected subgroup ($\text{UEFM} > 43$). This evidence of a negative relationship in milder patients resonates with classical findings that IHI is stronger in more impaired patients (Duque et al., 2005, Murase et al., 2004). On the other hand, our study has also found IHI to be reduced with lower UEFM in patients in the more-affected subgroup ($\text{UEFM} < 43$). This evidence of a positive relationship echoes findings of other studies that have suggested a more “forgiving” or supportive contralesional role in persons with more severe impairment (Bestmann et al., 2010, Sankarasubramanian et al., 2017). Overall, study of IHI-iSP across the severity spectrum has helped characterize the complexity of its relationship with impairment and helped draw appropriate conclusions about its role in the movement of the paretic upper limb.

Although evidence of a non-linear relationship between IHI-iSP and baseline impairment coincides with the bimodal theory, it differs from the findings of some other studies. Takeuchi et al. and Mang et al. have found this relationship to be linear, with IHI-iSP being reduced with more severe impairment (Mang et al., 2015, Takeuchi et al., 2010). The difference could be explained by limited numbers of patients in the range of moderate impairment (Mang et al., 2015) and different stroke patient population (Takeuchi et al., 2010). The direction of the relationship also differs from that observed in studies conducted by Harris-Love et al. (Harris-Love et al., 2016, Harris-Love et al., 2011). Harris-Love et al. have found IHI-iSP to be stronger with more severe impairment in patients with $\text{UEFM} < 42$, but in our more-affected subgroup ($\text{UEFM} < 43$) we have found IHI-iSP to be weaker with more severe impairment. Harris-Love et al. studied IHI-iSP for the biceps brachii muscle whereas we studied IHI-iSP for the FDI muscle. Differences in type of networks controlling proximal and distal muscles may explain observed differences (Cincotta et al., 2006, Inghilleri et al., 1997).

In addition to the relationships, impairment criterion identified here ($\text{UEFM} 43$) also aligns with the cutoffs derived from previous studies. Our previous study performed in a different sample of chronic stroke patients has found that with a cutoff of $\text{UEFM} 42$, less-affected and more-affected patients respond differently to inhibitory and facilitatory neuromodulation targeting the contralesional hemisphere (Sankarasubramanian et al., 2017). Inhibiting the contralesional motor cortices has a positive effect on reaching speed in less-impaired patients ($\text{UEFM} > 42$), while facilitating the contralesional motor cortices has a positive effect on reaching speed in more-impaired patients ($\text{UEFM} < 42$). With investigation of transcallosal influences, our present study has also arrived at similar conclusions and validated the previously identified impairment criterion ($\text{UEFM} 42$). Moreover, based on hierarchical cluster analysis, Woytowicz et al. also have identified a cutoff of $\text{UEFM} 42$ to separate patients with mild impairment from those with moderate/severe impairment (Woytowicz et al., 2017). The similarity between the criterion identified in the present study and those derived from previous clinical and neuromodulation studies lends confidence in the use for stratifying candidates for targeted treatment.

Our longitudinal findings further help confirm that the identified impairment criterion ($\text{UEFM} 43$) separates patient-subgroups differing on the basis of contralesional influence. Changes in IHI-iSP associated with motor improvement differ between patients less impaired than $\text{UEFM} 43$ and patients more impaired than $\text{UEFM} 43$. IHI-iSP reduces to a

greater degree among more impaired patients. This finding indicates that contralesional motor cortices potentially support paretic limb motor improvement in more-affected patients by reducing IHI-iSP on weak ipsilesional motor regions, thereby allowing better movement control. This result echoes previous findings that reduced inhibition from contralesional regions is associated with partially restored activation of weak ipsilesional motor regions and better movement control in more impaired individuals (Bestmann et al., 2010).

Recently, it has been argued that IHI is only a marker of the state of brain recovery instead of the reason behind chronic motor deficits (Xu et al., 2019). Therefore, it is debated whether IHI is even relevant to target in patients with stroke (Boddington and Reynolds, 2017). We maintain that reduction in IHI-iSP may still carry functional relevance. Patients less impaired than UEFM 43 who show greater reduction in IHI-iSP experience greater associated functional gains. Therefore, IHI reduction is a reasonable marker of restoration of their function. In patients more impaired than UEFM 43, lack of correlation with UEFM gains despite evidence of prominent IHI-iSP reduction suggests mechanisms of improvement may be more complex and remain to be understood. Changes in excitability of ipsilateral pathways or bifurcating spinal moto-neurons remain to be considered as other possible mechanisms of motor improvement (Carson, 2005, McCambridge et al., 2018).

IHI was measured using the iSP technique, instead of the classically used bi-hemispheric method (Duque et al., 2005, Murase et al., 2004). IHI measured by both iSP and bi-hemispheric methods is absent in patients with lesions or agenesis of corpus callosum, suggesting both methods characterize the inhibition involving transcallosal pathways. (Boroojerdi et al., 1996, Meyer et al., 1995, Meyer et al., 1998, Rothwell et al., 1991). Using the bi-hemispheric method, IHI can be tested at short-latency (6 – 15 ms) or long-latency intervals (40 – 50 ms) (Chen et al., 2003, Irlbacher et al., 2007). Short-latency IHI is believed to reflect activity of GABA_A-ergic networks, while long-latency IHI is believed to present activity of GABA_B-ergic populations (Irlbacher et al., 2007). IHI measured by the iSP method is similar to long-latency IHI measured by the bi-hemispheric method (Avanzino et al., 2007, Chen et al., 2003). Therefore, while IHI-L and IHI-iSP may represent similar mechanisms, IHI-S and IHI-iSP may be complementary but not identical for measurement of transcallosal inhibitory circuits (Avanzino et al., 2007, Chen et al., 2003). Differences in methods adopted to index IHI may also explain differences in evidence about the contralesional roles.

Finally, important caveats of our findings and limitations of methodology need to be considered. First, our sample size was small. The criterion identified here therefore still needs to be validated in a larger study. Second, although we identified an impairment criterion, criterion levels of residual corticospinal tract integrity (AMT and FA_{Asymmetry}) could not be identified. This is likely due to insufficient AMT data (unavailable in 4 patients who did not have any MEPs) and lack of adequate data in the severe range for FA_{Asymmetry}. DTI acquisition with two different scanners (due to replacement of institutional scanner) may also affect the data. Third, IHI-iSP of one subject was 3SD below group average at baseline (#12, IHI-iSP = 41.8%). Exclusion of this subject made the quadratic relationship even more robust ($R^2 = 0.531$ without #12 vs. $R^2 = 0.248$ with all subjects), and impairment criterion remained unchanged (UEFM 43). But despite their outlying value, this subject was

retained in analyses to capture variability of patient characteristics. Forth, mirror activity may have affected our IHI-iSP measurement. Mirror movements are common following stroke (Nelles et al., 1998) and are especially observed in severe patients during *tonic* muscle contraction (Calautti et al., 2007, Nelles et al., 1998). Since we encouraged subjects to maintain *tonic* contraction of the paretic FDI at 50% MVC, we found 8.9% ($\pm 16.3\%$) MVC (mirror) EMG in non-paretic FDI. However, this mirror EMG activity was not related to IHI-iSP captured from paretic FDI ($r = -0.244$, $p = 0.262$). Since mirror activity is natural to severe stroke and apparent during *tonic* muscle contraction required for iSP testing, excluding their effect here was not feasible and removing trials may significantly compromise iSP data analysis. Therefore, we chose to include all trials found to be valid for iSP measurement. Last, our results are specific to chronic patients. The original bimodal-balance recovery model was designed to predict future motor recovery based on interhemispheric balance and ipsilesional reserve assessed in the acute stage. In the present study, we extended the bimodal model and applied it in the chronic stage with some assumptions and flexibility. To provide direct evidence to support the bimodal model, future work may need to characterize how interhemispheric balance and ipsilesional reserve interact in acute phase and how these two variables predict the future recovery following stroke.

5. Conclusions

We have found that the relationship between IHI and baseline impairment is non-linear (quadratic) or ‘bimodal’. A criterion can be identified at impairment (UEFM) level of 43 with a 95% confidence interval between 40 and 46, such that patients less impaired than 43 show intense IHI with more severe impairment, whereas patients more impaired than 43 show reduced IHI with more severe impairment. The identified criterion has been further confirmed based on a longitudinal study, where stratified subgroups differ in how contralesional influence evolves with motor improvement following rehabilitation; patients more impaired than UEFM 43 show greater reduction in IHI than less impaired patients. Overall, the contralesional role varies in different severity ranges, which may be helpful to design targeted treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

IHI	inter-hemispheric inhibition
UEFM	Upper Extremity Fugl-Meyer

DTI	Diffusion Tensor Imaging
IHI	interhemispheric inhibition
TMS	transcranial magnetic stimulation
MCID	minimal clinically important difference
tDCS	transcranial direct current stimulation
FA	fractional anisotropy
PLIC	posterior limb of the internal capsule
FDI	first dorsal interosseous
RMT	resting motor threshold
AMT	active motor threshold
MVC	maximum voluntary contraction force
MEP	motor evoked potentials
iSP	ipsilateral silent period
IHI-iSP	interhemispheric inhibition measured with an ipsilateral silent period method
AIC	Akaike information criterion
ROC	receiver-operating characteristic
MSO	maximum stimulator output

References

- Avanzino L, Teo JT, Rothwell JC. Intracortical circuits modulate transcallosal inhibition in humans. *J Physiol* 2007;583(Pt 1):99–114. [PubMed: 17556392]
- Berglund K, Fugl-Meyer AR. Upper extremity function in hemiplegia. A cross-validation study of two assessment methods. *Scand J Rehabil Med* 1986;18(4):155–7. [PubMed: 3810081]
- Bestmann S, Swayne O, Blankenburg F, Ruff CC, Teo J, Weiskopf N, et al. The role of contralesional dorsal premotor cortex after stroke as studied with concurrent TMS-fMRI. *J Neurosci* 2010;30(36):11926–37. [PubMed: 20826657]
- Boddington LJ, Reynolds JN. Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. *Brain Stimul* 2017;10(2):214–22. [PubMed: 28117178]
- Boroogjerdi B, Diefenbach K, Ferbert A. Transcallosal inhibition in cortical and subcortical cerebral vascular lesions. *J Neurol Sci* 1996;144(1-2):160–70. [PubMed: 8994119]
- Bradnam LV, Stinear CM, Barber PA, Byblow WD. Contralesional hemisphere control of the proximal paretic upper limb following stroke. *Cereb Cortex* 2012;22(11):2662–71. [PubMed: 22139791]
- Calautti C, Naccarato M, Jones PS, Sharma N, Day DD, Carpenter AT, et al. The relationship between motor deficit and hemisphere activation balance after stroke: A 3T fMRI study. *Neuroimage* 2007;34(1):322–31. [PubMed: 17045490]
- Carson RG. Neural pathways mediating bilateral interactions between the upper limbs. *Brain Res Brain Res Rev* 2005;49(3):641–62. [PubMed: 15904971]

- Chen R, Yung D, Li JY. Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J Neurophysiol* 2003;89(3):1256–64. [PubMed: 12611955]
- Cincotta M, Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Inghilleri M, et al. Modulatory effects of high-frequency repetitive transcranial magnetic stimulation on the ipsilateral silent period. *Exp Brain Res* 2006;171(4):490–6. [PubMed: 16369790]
- Cunningham DA, Machado A, Janini D, Varnerin N, Bonnett C, Yue G, et al. Assessment of inter-hemispheric imbalance using imaging and noninvasive brain stimulation in patients with chronic stroke. *Arch Phys Med Rehabil* 2015a;96(4 Suppl):S94–103. [PubMed: 25194451]
- Cunningham DA, Varnerin N, Machado A, Bonnett C, Janini D, Roelle S, et al. Stimulation targeting higher motor areas in stroke rehabilitation: A proof-of-concept, randomized, double-blinded placebo-controlled study of effectiveness and underlying mechanisms. *Restor Neurol Neurosci* 2015b;33(6):911–26. [PubMed: 26484700]
- Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol* 2014;10(10):597–608. [PubMed: 25201238]
- Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther* 1983;63(10):1606–10. [PubMed: 6622535]
- Duque J, Hummel F, Celnik P, Murase N, Mazzocchio R, Cohen LG. Transcallosal inhibition in chronic subcortical stroke. *Neuroimage* 2005;28(4):940–6. [PubMed: 16084737]
- Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. *J Physiol* 1992;453:525–46. [PubMed: 1464843]
- Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Stegling S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med* 1975;7(1):13–31. [PubMed: 1135616]
- Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clin Neurophysiol* 2012;123(5):858–82. [PubMed: 22349304]
- Harris-Love ML, Chan E, Dromerick AW, Cohen LG. Neural substrates of motor recovery in severely impaired stroke patients with hand paralysis. *Neurorehabil Neural Repair* 2016;30(4):328–38. [PubMed: 26163204]
- Harris-Love ML, Morton SM, Perez MA, Cohen LG. Mechanisms of short-term training-induced reaching improvement in severely hemiparetic stroke patients: a TMS study. *Neurorehabil Neural Repair* 2011;25(5):398–411. [PubMed: 21343522]
- Inghilleri M, Cruccu G, Argenta M, Polidori L, Manfredi M. Silent period in upper limb muscles after noxious cutaneous stimulation in man. *Electroencephalogr Clin Neurophysiol* 1997;105(2):109–15. [PubMed: 9152203]
- Irlbacher K, Brocke J, Mechow JV, Brandt SA. Effects of GABA(A) and GABA(B) agonists on interhemispheric inhibition in man. *Clin Neurophysiol* 2007;118(2):308–16. [PubMed: 17174150]
- Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. *Proc Natl Acad Sci U S A* 2002;99(22):14518–23. [PubMed: 12376621]
- Jones DK, Knoösche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage* 2013;73:239–54. [PubMed: 22846632]
- Julious SA. Inference and estimation in a changepoint regression problem. *J Roy Stat Soc Ser D Statistician* 2001;50(1):51–61.
- Lindenberg R, Renga V, Zhu LL, Betzler F, Alsop D, Schlaug G. Structural integrity of corticospinal motor fibers predicts motor impairment in chronic stroke. *Neurology* 2010;74(4):280–7. [PubMed: 20101033]
- Lotze M, Markert J, Sauseng P, Hoppe J, Plewnia C, Gerloff C. The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. *J Neurosci* 2006;26(22):6096–102. [PubMed: 16738254]
- Lowe MJ, Beall EB, Sakaie KE, Koenig KA, Stone L, Marrie RA, et al. Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity. *Hum Brain Mapp* 2008;29(7):818–27. [PubMed: 18438889]

- Mang CS, Borich MR, Brodie SM, Brown KE, Snow NJ, Wadden KP, et al. Diffusion imaging and transcranial magnetic stimulation assessment of transcallosal pathways in chronic stroke. *Clin Neurophysiol* 2015;126(10):1959–71. [PubMed: 25631612]
- McCambridge AB, Stinear JW, Byblow WD. Revisiting interhemispheric imbalance in chronic stroke: A tDCS study. *Clin Neurophysiol* 2018;129(1):42–50. [PubMed: 29145166]
- McDonnell MN, Stinear CM. TMS measures of motor cortex function after stroke: A meta-analysis. *Brain Stimul* 2017;10(4):721–34. [PubMed: 28385535]
- Meyer BU, Roricht S, Graf von Einsiedel H, Kruggel F, Weindl A. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 1995;118 (Pt 2):429–40. [PubMed: 7735884]
- Meyer BU, Roricht S, Woiciechowsky C. Topography of fibers in the human corpus callosum mediating interhemispheric inhibition between the motor cortices. *Ann Neurol* 1998;43(3):360–9. [PubMed: 9506553]
- Mohapatra S, Harrington R, Chan E, Dromerick AW, Breceda EY, Harris-Love M. Role of contralesional hemisphere in paretic arm reaching in patients with severe arm paresis due to stroke: A preliminary report. *Neurosci Lett* 2016;617:52–8. [PubMed: 26872851]
- Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 2004;55(3):400–9. [PubMed: 14991818]
- Nelles G, Cramer SC, Schaechter JD, Kaplan JD, Finklestein SP. Quantitative assessment of mirror movements after stroke. *Stroke* 1998;29(6):1182–7. [PubMed: 9626292]
- Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther* 2012;92(6):791–8. [PubMed: 22282773]
- Perez MA, Butler JE, Taylor JL. Modulation of transcallosal inhibition by bilateral activation of agonist and antagonist proximal arm muscles. *J Neurophysiol* 2014;111(2):405–14. [PubMed: 24155008]
- Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. *Clin Rehabil* 2005;19(4):404–11. [PubMed: 15929509]
- Plow EB, Carey JR, Nudo RJ, Pascual-Leone A. Invasive cortical stimulation to promote recovery of function after stroke: a critical appraisal. *Stroke* 2009;40(5):1926–31. [PubMed: 19359643]
- Plow EB, Cunningham DA, Beall E, Jones S, Wyant A, Bonnett C, et al. Effectiveness and neural mechanisms associated with tDCS delivered to premotor cortex in stroke rehabilitation: study protocol for a randomized controlled trial. *Trials* 2013;14:331. [PubMed: 24119615]
- Potter-Baker KA, Varnerin NM, Cunningham DA, Roelle SM, Sankarasubramanian V, Bonnett CE, et al. Influence of corticospinal tracts from higher order motor cortices on recruitment curve properties in stroke. *Front Neurosci* 2016;10:79. [PubMed: 27013942]
- Puig J, Pedraza S, Blasco G, Daunis IEJ, Prados F, Remollo S, et al. Acute damage to the posterior limb of the internal capsule on diffusion tensor tractography as an early imaging predictor of motor outcome after stroke. *AJNR Am J Neuroradiol* 2011;32(5):857–63. [PubMed: 21474629]
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120(12):2008–39. [PubMed: 19833552]
- Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 1994;91(2):79–92. [PubMed: 7519144]
- Rothwell J, Colebatch J, Britton T, Priori A, Thompson P, Day B, et al. Physiological studies in a patient with mirror movements and agenesis of the corpus-callosum. *J Physiol* 1991;438:34P.
- Sakaie KE, Lowe MJ. An objective method for regularization of fiber orientation distributions derived from diffusion-weighted MRI. *Neuroimage* 2007;34(1):169–76. [PubMed: 17030125]
- Sakaie KE, Lowe MJ. Quantitative assessment of motion correction for high angular resolution diffusion imaging. *Magn Reson Imaging* 2010;28(2):290–6. [PubMed: 19695824]

- Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Phys Ther* 1993;73(7):447–54. [PubMed: 8316578]
- Sankarasubramanian V, Machado AG, Conforto AB, Potter-Baker KA, Cunningham DA, Varnerin NM, et al. Inhibition versus facilitation of contralesional motor cortices in stroke: Deriving a model to tailor brain stimulation. *Clin Neurophysiol* 2017;128(6):892–902. [PubMed: 28402865]
- Sidaros A, Engberg AW, Sidaros K, Liptrot MG, Herning M, Petersen P, et al. Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain* 2008;131(Pt 2):559–72. [PubMed: 18083753]
- Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain* 2007;130(1):170–80. [PubMed: 17148468]
- Sundgren PC, Dong Q, Gómez-Hassan D, Mukherji SK, Maly P, Welsh R. Diffusion tensor imaging of the brain: review of clinical applications. *Neuroradiology* 2004;46(5):339–50. [PubMed: 15103435]
- Takeuchi N, Tada T, Toshima M, Ikoma K. Correlation of motor function with transcallosal and intracortical inhibition after stroke. *J Rehabil Med* 2010;42(10):962–6. [PubMed: 21031294]
- Wolf SL, Thompson PA, Morris DM, Rose DK, Winstein CJ, Taub E, et al. The EXCITE trial: attributes of the Wolf Motor Function Test in patients with subacute stroke. *Neurorehabil Neural Repair* 2005;19(3):194–205. [PubMed: 16093410]
- Woytowicz EJ, Rietschel JC, Goodman RN, Conroy SS, Sorkin JD, Whittall J, et al. Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke. *Arch Phys Med Rehabil* 2017;98(3):456–62. [PubMed: 27519928]
- Xu J, Branscheidt M, Schambra H, Steiner L, Widmer M, Diedrichsen J, et al. Rethinking interhemispheric imbalance as a target for stroke neurorehabilitation. *Ann Neurol* 2019;85(4):502–13. [PubMed: 30805956]
- Zhang M, Sakaie KE, Jones SE. Logical foundations and fast implementation of probabilistic tractography. *IEEE Trans Med Imaging* 2013;32(8):1397–410. [PubMed: 23568498]
- Zhu LL, Lindenberg R, Alexander MP, Schlaug G. Lesion load of the corticospinal tract predicts motor impairment in chronic stroke. *Stroke* 2010;41(5):910–5. [PubMed: 20378864]

Highlights

- The relationship between interhemispheric inhibition and motor impairment is nonlinear (bimodal).
- We have defined a criterion of Upper Extremity Fugl-Meyer score of 43, which can be used for designing tailored treatments.
- Our results are in line with the bimodal-balance recovery model.

Figure 1.

Example of the ipsilesional silent period (iSP) data used to characterize interhemispheric inhibition (IHI-iSP) from the contralesional motor cortex in a stroke patient, using transcranial magnetic stimulation (TMS). (A) Schematic describes how iSP is collected based on application of supra-threshold (150% contralesional resting motor threshold, RMT). TMS pulses to the contralesional hemisphere during contraction of the paretic first dorsal interosseous (FDI) muscle. (B) Example traces showing how TMS leads to transient suppression (silence) of ongoing paretic FDI activity in a patient with Upper Extremity Fugl-Meyer (UEFM) of 53. Onset and offset of iSP are marked (*top*). Onset is at 47 ms after the application of the TMS pulse in this example and 22 ms later than the onset of the contralateral motor evoked potential (MEP) (*bottom*). iSP lasted for 31 ms and showed a 72% reduction in EMG (relative to pre-stimulus EMG). The reduction was used to characterize IHI.

Figure 2.

All the relationships between baseline IHI-iSP and impairment/damage are quadratic. (A) The threshold regression model for UEFM was significant and the criterion UEFM level could be identified at 43 (95% confidence interval: 40 to 46). (B) The change point of AMT is at 65% but the threshold regression model was not significant. (C) The change point of FA_{Asymmetry} is at 0.22 but the threshold regression model was not significant. (D) Patient with UEFM of 44 demonstrates stronger IHI-iSP (81% decrease in paretic FDI EMG) (*left*) than another patient with milder impairment (UEFM = 54) (61% decrease in paretic FDI EMG) (*right*). IHI-iSP, interhemispheric inhibition measured with the method of ipsilateral silent period; UEFM, Upper Extremity Fugl-Meyer; AMT, active motor threshold; iSP, ipsilateral silent period; FA_{Asymmetry}, fractional anisotropy asymmetry; FDI, first dorsal interosseous.

Figure 3.

(A) IHI-iSP of healthy control subjects and IHI-iSP at baseline and post-training for patients less affected and more affected than UEFM 43. At post-training, there is a significant difference in IHI-iSP between less-affected and more-affected patients. (B) Pre- to post-treatment change in IHI-iSP is compared a more-affected patient (UEFM = 36) (*left*) to a less-affected patient (UEFM = 60) (*right*). The more-affected patient shows more substantial reduction in IHI from pre- to post-treatment compared to the less affected patient (–12% vs. 3%). (C and D) Correlation between change in IHI-iSP and change in UEFM is not significant in the more-affected subgroup ($p = 0.996$) but is significant in less-affected subgroups ($p = 0.009$). IHI-iSP, interhemispheric inhibition measured with the method of ipsilateral silent period; UEFM, Upper Extremity Fugl-Meyer.

Table 1.

Subject Characteristics

Subject	Age/Gender/ Handedness	Time post Stroke (Months)	Side of Paresis	Lesion Location	Lesion Volume (cm ³)	UEFM (Max 66)	Ipsi- AMT (%)	FA Asymmetry	iSP (%)
1[‡]	68/F/R	32	L	Basal ganglia	2.2	35	83	0.103	N/A
2[‡]	66/M/R	19	L	Cortical (frontal)	9.4	50	73	-0.001	67.5
3	72/M/R	45	L	IC, putamen, Cortical (temporal, frontal)	49	19	— [‡]	0.291	66.1
4	58/F/L	24	L	Caudate nucleus, basal ganglia	2.8	54	60	0.189	69.5
5	69/M/R	23	R	Thalamus, IC	1.5	46	34	0.059	72.1
6[‡]	54/M/R	29	R	Caudate nucleus, basal ganglia	2.4	44	38	0.196	80.2
7	72/M/R	84	L	Pontine, mesencephalus	0.01	59	30	-0.017	60.9
8[‡]	55/F/R	48	R	Thalamus, IC	1.8	47	38	0.068	66.9
9	59/F/R	23	L	Temporal lobe, basal ganglia, caudate nucleus	80.8	51	40	0.590	69.1
10[‡]	76/M/R	24	R	Basal ganglia, IC, corona radiata	0.9	15	100	0.054	60.6
11	50/M/R	54	L	Thalamus, IC	1	44	40	0.106	76.7
12	45/M/R	12	R	Temporal lobe, IC	60.7	26	95	0.560	41.8
13[‡]	63/M/R	228	R	Cortical (frontal, parietal), caudate nucleus, IC, striatum, central semiovale	48.6	53	40	0.094	67.6
14	55/M/A	38	R	IC, putamen	0.4	58	42	0.104	66.3
15	55/M/R	48	R	Corona radiata, putamen, IC	1.2	22	— [‡]	0.180	69.3
16[‡]	76/M/R	101	R	Corpus callosum, IC, thalamus, putamen	0.2	57	34	0.012	69.8
17[‡]	56/M/L	13	L	Caudate nucleus, putamen, thalamus, IC	0.3	59	47	-0.005	63.3
18[‡]	53/M/R	34	R	Caudate, IC [*]	N/A [*]	36	60		70.9
19	55/M/R	45	R	Corona radiata, IC, thalamus, putamen	1.4	29	— [‡]	0.109	74.9
20	77/M/R	84	R	Caudate nucleus, corona radiata, IC, putamen	1	43	65	0.216	80.6
21[‡]	58/F/L	57	R	Putamen, IC, corona radiata, thalamus	1.5	30	49	0.131	67.5
22	69/M/R	22	R	IC, putamen	1.2	42	— [‡]	-0.021	75.1
23	62/M/R	11	R	IC, putamen, caudate nucleus	0.1	65	37	0.027	64.0

Subject	Age/Gender/ Handedness	Time post Stroke (Months)	Side of Paresis	Lesion Location	Lesion Volume (cm ³)	UEFM (Max 66)	Ipsi- AMT (%)	FA Asymmetry	iSP (%)
24	57/M/R	19	R	IC	0.2	54	80	-0.004	60.6
Mean ± SD	61.7 ± 8.9 5(F), 20 (R)	45.6 ± 45.4	16 (R)	--	11.7 ± 23.3	43.6 ± 13.9	54.3 ± 21.6	0.132 ± 0.162	67.9 ± 8.0
Control (n=11)	63.8 ± 11.7 6(F), 11 (R)	--	--	--	--	--	34.6 ± 6.8	-0.002 ± 0.044	66.7 ± 5.4

* Magnetic resonance imaging (MRI) was not performed due to report of claustrophobia and lesion location is based on medical chart

[†] Motor evoked potential could not be elicited

[‡] Marked subject numbers indicates the subjects received tDCS combined with rehabilitation, while the other subjects had sham and rehabilitation

[§] Significant difference between patient and control groups ($p < 0.05$); M, male; F, female; R, right side; L, left side; UEFM, Upper Extremity Fugl-Meyer; Ipsi-AMT, ipsilesional active motor threshold; FA Asymmetry, fractional anisotropy asymmetry; iSP, ipsilateral silent period; IC, internal capsule.

Results of likelihood test and goodness of fit of linear and quadratic regression models, using R^2 and Akaike information criterion (AIC)

Table 2.

		Likelihood test [*]			Linear regression			Quadratic regression			Type of relationship
		<i>F</i>	<i>p</i>		R^2	AIC		R^2	AIC		
iSP	UEFM	6.346	0.020		0.009	98.398		0.248	94.060		Quadratic [‡]
	AMT	5.003	0.040		0.251	78.656		0.429	75.486		Quadratic [‡]
	FA _{asymmetry}	6.307	0.021		0.062	93.922		0.296	89.616		Quadratic [‡]

^{*} Likelihood test examined the difference in goodness of fit between linear and quadratic models with level of significance set at 0.05.

[‡] The likelihood test was significant, so R^2 and AIC were used to determine whether linear or quadratic models provide better goodness of fit (greater R^2 and less AIC)

[§] iSP, ipsilateral silent period; UEFM, Upper Extremity Fugl-Meyer; AMT, active motor threshold; FA_{asymmetry}: fractional anisotropy asymmetry