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Non-paretic arm force does not over-inhibit the paretic arm in chronic post-stroke hemiparesis

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Abstract

Objective—To determine whether non-paretic arm force over-inhibits the paretic arm in patients with chronic unilateral post-stroke hemiparesis. We hypothesized that interhemispheric inhibition would increase more in healthy controls than in hemiparetic patients.

Design—Case-control neurophysiologic and behavioral study of patients with chronic stroke.

Setting—Federal research institution, outpatient clinical research setting

Participants—Eighty-six referred patients were screened to enroll 9 participants with greater than 6 month history of one unilateral ischemic infarct that resulted in arm hemiparesis, with residual ability to produce 1Nm of wrist flexion torque, without contraindication to transcranial magnetic stimulation. 8 age- and handedness-matched healthy volunteers without neurologic diagnosis were studied for comparison.

Interventions—Not Applicable

Main Outcome Measures—Change in interhemispheric inhibition targeting the ipsilesional primary-motor-cortex (M1) during non-paretic arm force.

Results—Healthy age-matched controls had significantly greater increases in inhibition from their active to resting M1 than did stroke patients from their active contralesional to resting ipsilesional M1 in the same scenario ($20\% \pm 7$ vs. $-1\% \pm 4$, $F_{1,12}=6.61$, $p=0.0245$). Patients with greater increases in contralesional to ipsilesional inhibition were better performers on the nine-hole-peg-test of paretic arm function.

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Conclusions—Our findings reveal that producing force with the non-paretic arm does not necessarily over-inhibit the paretic arm. Though limited in generalizability by the small sample size, we found that greater active contralesional to resting ipsilesional M1 inhibition was related to better recovery in this subset of chronic post-stroke patients.

Keywords

Stroke; Neurophysiology; Hemiparesis

Motor performance of unimanual and bimanual tasks requires a balanced interaction between the two hemispheres of the brain.¹ Following a stroke, however, the diaschisis between brain areas, i.e., the abnormal function of brain areas either directly connected or remote from the stroke-damaged area, is thought to negatively impact motor control. While post-stroke diaschisis has been well described and shown to relate to function^{2–4}, the direct effects on motor physiology and recovery are not well understood. The impairment in interhemispheric interactions may be critical to recovery from post-stroke paralysis,⁵ yet it is inadequately understood from the perspective of physiological mechanisms. Some forms of rehabilitation including mirror and bimanual therapy are based on a model of cooperative interactions between the two hemispheres^{6, 7}. On the other hand, another model argues that the non-paretic M1 may over-inhibit the paretic M1 and hinder post-stroke motor rehabilitation.^{8–10} The latter model has been used to design interventions, such as brain stimulation and non-paretic constraint, to inhibit the non-paretic corticospinal system to enhance rehabilitation. However, the benefits of inhibiting the non-paretic arm have been modest at best¹¹.

One possible reason for the modest effect of these strategies may be that the current model of interhemispheric competition is incomplete, being limited to averaged interactions across time or studied primarily during paretic arm activity¹¹. Therefore, a remaining question is how non-paretic arm activity affects interhemispheric inhibition (IHI) targeting the ipsilesional M1. The objective of this study was to determine whether non-paretic arm force over-inhibits the paretic arm in patients with chronic unilateral post-stroke hemiparesis. Based on previous findings in healthy participants, we hypothesized that interhemispheric inhibition would increase more in healthy controls than in hemiparetic patients¹².

Methods

Ethical Approval

All participants provided written informed consent under protocols approved by the National Institute of Neurological Disorders and Stroke Intramural Institutional Review Board in accordance with the Declaration of Helsinki.

Participants

Eighty-six stroke patients were screened for this study. Nine patients (average age 62, range 46–80) with post-stroke hemiparesis met the following inclusion criteria and were enrolled:

1. one episode of ischemic stroke occurring six-months or more prior to enrollment

2. anatomic MRI confirmation of stroke, excluding involvement of the brainstem or cerebellum
3. lack of contraindication to transcranial magnetic stimulation (TMS) or magnetic resonance imaging (MRI) consistent with international guidelines¹³
4. ability to produce wrist flexion 1Nm of torque with the paretic arm
5. adequate cognitive function to participate in experimental sessions
6. lack of other medical or neurologic illness that would impair ability to participate.

Although we did not have a measure of spasticity in these patients, all of the patients had to be able to produce wrist flexion torque of at least 1Nm with their paretic arm and relax in between trials, which excluded participants with significant amounts of spasticity. Patient characteristics are listed in Table 1. MRI scans of the brain were obtained for each patient for lesion localization (3 Tesla scanner; T1 scan: TR 6.272s, TE 2.672s, FOV: 240×240, Dimensions: 0.9375×0.9375×1mm; T2 scan: TR 8500s, TE 122.192s, FOV: 240.0256×240.0256, Dimensions: 0.4688×0.4688×1.5mm)^c. Lesion masks were hand drawn for each patient (M.A.D.)^d, and then cost-function-masked normalization of each patient's MRI and lesion mask was done to create a lesion overlap map^{d,e} using previously described techniques (Figure 1)^{14, 15}. The nine-hole-peg-test (NHPT)¹⁶ was used to obtain a measure of paretic arm function. The NHPT required participants to move 9 pegs from a shallow bowl to one of nine holes as quickly as possible. Each participant completed this task 6 times alternating between the paretic and non-paretic arm. The times were averaged and the NHPT score was calculated (1 – non-paretic/paretic). Seven of the 9 patients were able to complete the NHPT. A group of 8 healthy controls were also recruited for comparison. The healthy controls were matched to the stroke group for age (average age 66, range 40–82), pre-morbid handedness (1 left handed in each group), and gender (4 females in each group).

Experimental Design

Subjects sat in an ergonomic dental chair watching a computer display. Surface EMG was recorded via two 7mm diameter Ag-AgCl electrodes, placed over the belly of the flexor carpi radialis (FCR) muscles bilaterally, with a 2cm inter-electrode distance¹⁷, with a ground electrode placed on the dorsum of the resting hand. The signal was amplified, band pass filtered (2Hz–500Hz), digitally sampled at 2kHz, recorded and displayed via computer^f. The **resting arm** was placed in the most comfortable position for the participant to reduce involuntary activity in the FCR muscle. The **active arm** was placed in a custom arm manipulandum with soft restraints, the palm of the hand positioned against a joystick connected to a six-degree-of-freedom load cell^a. The device was designed to isolate wrist flexion from more proximal arm movements¹⁸. Maximum voluntary contraction (MVC) levels were determined by instructing subjects to produce isolated and isometric wrist flexion for approximately 3 seconds. MVC for each arm was determined by averaging torque from 3 trials.

Following the MVCs, TMS was used to determine the hotspots, resting motor thresholds (rMT), and maximum motor evoked potentials amplitudes for FCR in both arms¹⁹. We used

double coils (standard 70mm for the Test Stimulus or custom 60mm for the Conditioning Stimulus in order to fit 2 coils on the participant scalp) to deliver TMS. Pulses were generated by 3 monophasic magnetic stimulators, 2 of which were connected through a connecting module^b. Following the initial assessment with TMS, participants completed the experimental protocol.

Experiment 1

Overall experimental design for post-stroke participants consisted of obtaining 3 Physiologic Measures under 2 Scenarios, 3 Conditions. All Physiological Measures, Scenarios, and Conditions were randomized in order across subjects. In Scenario 1 patients activated the non-paretic arm, while the paretic arm was completely at rest for all conditions. Scenario 2 was the opposite with patients activating the paretic arm and keeping the non-paretic arm at rest for all conditions. Since healthy adult controls don't have paretic and non-paretic arms, they only participated in 1 Scenario. The 3 Conditions were: 1) 0% (rest) in which the participant watched the screen but did not perform isometric wrist contraction with either arm, 2) 10%, where the active arm produced isometric wrist flexor contraction at 10% of MVC, and 3) 70% where the active arm produced isometric wrist flexor contraction at 70% of MVC. In all trials, the resting arm FCR EMG was monitored to ensure that no mirror activity occurred.

In the 10% and 70% conditions, each trial started with a go signal, and the force induced by wrist flexion was visually displayed as a cursor moving horizontally towards the target force zone. Physiologic measurements were made while the cursor was within the required target force zone for the force conditions and at any time for the 0% condition. At the end of each trial the subject relaxed until the next go signal. Trials were completed as a block of 10 of the same condition with an inter-trial interval of 5s with 20% jitter, and an inter-block resting period of 1–3 minutes. Subjects were instructed before each block whether they would be exerting 0%, 10% or 70% of MVC, and the presentation of the conditions was randomized. Three blocks were completed per condition, per physiologic measure, so that a total of 30 samples of each physiologic measure were made for each condition. Trials with involuntary or mirror muscle activity in the resting FCR were aborted and repeated once the subject was able to reduce the background activity.

Physiologic Measures

Physiologic measures were obtained from the resting FCR via surface EMG. All measures are taken on peak to peak amplitude of the motor evoked potential evoked by TMS.

Physiologic Measure 1: Interhemispheric Inhibition (IHI): To measure IHI, we used a well described paired conditioning-test pulse protocol at 10ms inter-stimulus-interval matched for stimulus intensity across force conditions²⁰. Briefly, a conditioning pulse at suprathreshold intensity to the active M1 evokes the 10ms-contralateral-conditioning-stimulus-motor-evoked-potential, (CCS10-MEP)²¹, a measure of corticospinal excitability in the active arm, with a unit of mV. The TMS coil is positioned with the handle at 90 degrees to the midsagittal line for this measure. This stimulation not only evokes the CCS10-MEP, but through transcallosal circuits also inhibits the motor evoked potential produced by the test-

stimulus delivered 10ms later to the opposite resting M1 (TS-MEP), also measured in mV. The coil is placed with handle posterior and 45 degrees to the mid-sagittal line for TS-MEP. The ratio of the conditioned MEP to the TS-MEP amplitude multiplied by 100 gives IHI.²²

Physiologic Measure 2: Short-interval intracortical inhibition (SICI): To test local inhibitory circuits within the resting M1 we used a standard protocol for SICI with an interstimulus interval of 2ms²³. Briefly, both the conditioning and test pulse are delivered to the same M1. The conditioning pulse, delivered at subthreshold intensity does not produce any MEP, but followed 2ms later by a TS, produces an inhibited MEP relative to the TS-MEP, measured in mV. SICI was reported as the ratio of the inhibited MEP to the TS-MEP multiplied by 100.

Physiologic Measure 3: was excitability of the resting arm, obtained via the TS-MEP. The TMS intensity was set at a level required to elicit a TS-MEP amplitude at rest of approximately 200 – 500 μ V, as previously reported for this muscle^{24, 25}.

Thirty samples of each measure, IHI, SICI, and TS-MEP, were obtained from the rest arm in each force condition. In two patients IHI, SICI and TS-MEP were characterized over 20 trials due to inability to maintain relaxation. Both SICI and IHI vary depending on the level of the conditioning stimulus. For SICI, the amount of inhibition induced is usually in the shape of a U-curve with regards to conditioning stimulus intensity, while IHI it is sigmoidal. We adjusted conditioning stimulus intensities to aim for SICI and IHI of approximately 50% during the 0% condition. Theoretically, this would allow for the two force conditions to alter SICI and IHI in either a positive or negative direction and would avoid floor or ceiling effects, as previously reported²⁵. Also, for all measures, the TS-MEP amplitude was matched throughout all trials and conditions as previously recommended²¹.

Experiment 2

Additionally, we measured IHI when CCS10-MEP amplitudes at rest and 70% MVC were matched (IHic) in 5 patients in whom it was feasible^{21, 25}.

Experiment 3

Healthy, age-matched controls took part in Scenario 1, with physiologic measures being recorded from the resting non-dominant arm while the dominant arm produced isometric wrist flexor contractions. In this Scenario, results from the healthy controls act as a comparison to patients producing force with their non-paretic arm.

Data Analysis

All measures of motor evoked potentials (MEP) are reported in mV. All measures of cortical inhibition, which are ratios of inhibited motor evoked potentials compared to baseline motor evoked potentials, are reported in percentage. For IHI, IHic, SICI, which are ratios, we subtracted: $A - B$ where B is the mean during the Force Condition (10% or 70% MVC) and A is the mean at baseline 0% MVC to produce %changeIHI, %changeIHic, and %changeSICI. For TS-MEP and CCS10-MEP, which express absolute amplitudes (mV), we calculated force-induced percent change: $(A - B)/A$ where B is the mean during the Force Condition (10% or 70% MVC) and A is the mean at baseline 0% MVC to produce

%changeMEP and %changeCCS10-MEP. Positive %changeMEP and %changeCCS10-MEP thus reflect larger MEP amplitudes with force while positive %changeIHI, %changeIHlc, and %changeSICI reflect greater inhibition with force. To determine if %changeCCS10-MEP's relationship to %changeIHI was dependent on which arm in which it was recorded (paretic vs. non-paretic) we calculated: $A - B$ where A is the value in the non-paretic arm and B is the value in the paretic arm to produce %changeCCS10-MEP-DIFF and %changeIHI-DIFF.

Statistical Analysis

To test the primary objective, whether non-paretic arm force over-inhibits the paretic arm in patients with chronic unilateral post-stroke hemiparesis, IHI targeting the resting paretic arm during active non-paretic arm force was compared to healthy controls. Two multivariate analysis of variance (MANOVA) models were used to examine the interactions between GROUP (Stroke or Healthy Control) and FORCE (10% or 70%) and then to test the two main effects, with an assumed compound symmetric covariance structure to take into account correlations between measurements per participant. In a secondary analyses, the interaction between ARM (Paretic or Non-Paretic) and FORCE (10% or 70%) within stroke patients, and ARM or FORCE without the interaction term was analyzed on each of the measures (%changeIHI, %changeMEP, %changeSICI, %changeIHlc). In both models, an unstructured covariance matrix was assumed to incorporate correlations among the four measurements per participant.

In the stroke patients, to test whether differences in %changeIHI were due to differences in %changeCCS10MEP, we used multivariate analysis of covariance (MANCOVA) to examine the interactions between %changeIHI-DIFF, %changeCCS10MEP-DIFF, and FORCE. The MANCOVA model contained FORCE as a factor and %changeCCS10MEP-DIFF as a covariate as well as the FORCE by %changeCCS10MEP-DIFF interaction with a compound symmetric covariance matrix. A Spearman's rank correlation coefficient was used to investigate the correlation between %changeCCS10MEP-DIFF and %changeIHI-DIFF in each force condition.

Further control analyses (unpaired t-tests) were also performed to ensure that TS-MEP amplitudes were controlled between conditions and that baseline 0% MVC measures were comparable between paretic and non-paretic arms (Table 2). Finally, a robust regression was used to analyze the relationship between non-paretic to paretic %changeIHI in the 70% MVC condition and paretic arm function (Nine-Hole-Peg-Test)²⁶. Primary analyses were implemented in SAS PROC Mixed with $\alpha=0.05^g$ except for the robust regression which was implemented in Prism 5^h. Data are described as mean $\pm$ SE.

Results

All subjects were able to complete the experimental procedures without adverse effects. Two participants could not perform the NHPT due to lack of motor control in the fingers but were still able to participate in the experiment since they could produce at least 1Nm of wrist flexor torque. There were no differences in age between the healthy controls and the participants with stroke ($t_{15}=0.29$, $P=0.78$). Finally, significant differences in our measures

of interest were not due to inadequate control of baseline measures or poor matching of baseline MEP amplitudes (Table 2).

Main Physiologic Measure: Non-paretic to Paretic Arm Inhibition Compared to Healthy Controls

Healthy age-matched controls had significantly greater increases in inhibition from their active to resting arms than did stroke patients from their non-paretic to paretic arms in Scenario 1 (%changeIHI: $20\% \pm 7$ vs. $-2\% \pm 4$, $F_{1,12}=6.61$, $p=0.0245$). See Figure 2. Resting arm excitability also increased more in healthy volunteers compared to the resting paretic arm of stroke patients ($90\% \pm 3$ vs. $24\% \pm 13$, $F_{1,14}=5.54$, $p=0.0337$) and there was a non-significant trend towards greater reduction in local inhibition in healthy volunteers compared to the resting paretic arm of stroke patients ($-41\% \pm 13$ vs. $-11\% \pm 7$, $F_{1,13}=3.46$, $p=0.0856$). Overall, in stroke patients there was an under-inhibition from the active non-paretic arm to resting paretic arm and an associated lack of modulation in other measures compared to healthy controls.

Secondary Physiologic Measures: Comparing paretic arm force to non-paretic arm force

Comparing Scenario 1 to Scenario 2 in stroke patients, interhemispheric inhibition and the resulting changes in excitability in the resting arm were all significantly different, with changes in the non-paretic arm all being greater than in the paretic arm (%changeIHI: $16\% \pm 8$ vs. $-2\% \pm 4$, $F_{1,7}=6.53$, $p=.0378$; %changeSICI: $-28\% \pm 7$ vs. $-11\% \pm 7$, $F_{1,8}=34.07$, $p=.0004$, MEP: $116\% \pm 24$ vs. $24\% \pm 13$, $F_{1,8}=8.47$, $p=.0196$) (Figure 2). Incidentally, excitability in the resting arm also showed an effect of Condition where 70%MVC induced greater change in excitability than 10%MVC ($81\% \pm 19$ vs. $52\% \pm 16$, $F_{1,8}=6.26$, $p=0.0368$). There was no significant interaction between ARM and FORCE for any of the measures (%changeIHI ($F_{1,7}=0.18$, $p=0.6841$), %changeSICI ($F_{1,8}=0.17$, $p=0.6948$), %changeMEP ($F_{1,8}=0.31$, $p=0.5906$)).

Origin of Abnormal %changeIHI

The difference in inhibition between Scenario 1 and Scenario 2 in stroke patients may theoretically originate in the sending or receiving circuits. We looked at how force changed the excitability in the active arm (%changeCCS10-MEP-DIFF) and measured whether that could explain the differences in inhibition (%changeIHI-DIFF). No correlation between %changeCCS10-MEP-DIFF and %changeIHI-DIFF was found for either force Condition (Spearman's Rank Correlation Coefficient: 10%: $r = 0.4643$, $p = 0.2939$, 70%: $r = -0.5714$, $p = 0.1802$). To further test the influence of corticospinal excitability in the sending corticospinal system on force-induced inhibition, we tested %changeIHIC (see Methods) ^{21, 25, 27} and found no effect of ARM ($F_{1,4}=2.49$, $p=0.1898$). Thus, we found no evidence that the abnormality in modulation of inhibition targeting the paretic arm depends on impaired force-induced recruitment of transcallosal drive.

Clinical Correlation

A robust regression revealed a positive relationship between paretic arm performance on the Nine-Hole-Peg-Test (NHPT) and increases in inhibition from the active non-paretic to resting paretic arm (Figure 3)

Discussion

The results from this study highlight novel findings and expand on previous studies. First, our findings reveal that producing force with the non-paretic arm does not necessarily over-inhibit the paretic arm in patients with chronic post-stroke hemiparesis as previously assumed. In healthy subjects, inhibition from the active to the resting arm actually increases more during unimanual force, and is associated with increasing excitability in the resting arm, likely due to the summative effects of interhemispheric inhibition on local excitability^{27–30}. Consistent with those previous studies, we found that in our elderly healthy controls, force induced increases in inhibition from the active to the resting arm accompanied by decreases in local inhibition sum to increase corticospinal excitability on the resting M1. In stroke patients producing non-paretic force, though, a task-dependent abnormality in transcallosal interactions, not present at rest, may contribute to the absence of facilitation in paretic arm excitability during non-paretic force³¹.

Secondly, these results provide novel evidence that post-stroke abnormalities in interhemispheric inhibition are task dependent with regards to non-paretic arm activity, rather than static, consistent with previous studies^{8–10, 27–30, 32}. Finally, greater non-paretic to paretic inhibition was related to better recovery in chronic post-stroke patients. The positive relationship between inhibition and paretic arm performance suggests that the integrity of physiologic mechanisms between the two arms relate to post-stroke upper extremity function.

Taken together, these findings have important implications for neurorehabilitation efforts for survivors of stroke, though our small sample size may limit the generalizability of the findings. Specifically, they raise the hypothesis that interventions designed to alter the activity of the non-paretic arm need to be tailored to the millisecond by millisecond changes in brain network interactions during different motor behaviors rather than just being applied statically. This concept has been insufficiently studied in the neurorehabilitation literature.

Producing force with non-paretic arm does not over-inhibit the paretic arm

Since our results demonstrated normal increases in corticospinal excitability in both the paretic arm and non-paretic arm with force, but differences between the two arms in recruitment of transcallosal inhibition, they were consistent with a previously described model of two groups of corticofugal neurons²¹. Thus, transcallosal circuits may change differently than the corticospinal circuitry after stroke. Our results may also help explain the detrimental effects³³ or low effect size sometimes reported for interventions that reduce excitability within the non-paretic arm¹¹.

This task-dependent abnormality in transcallosal interactions, not present at rest, may contribute to the absence of facilitation in paretic arm excitability during non-paretic arm

force³¹. Paretic arm local inhibition did not decrease during non-paretic force, an abnormality that is both different from what has been found in young healthy controls and separate from what has been described as a baseline of lower local inhibition post-stroke^{25,34, 35}. This persistence in paretic local inhibition may also help explain the lack of force-induced increases in overall corticospinal excitability in the paretic arm³¹.

Finally, in trying to understand where the abnormality in non-paretic to paretic-arm inhibition arises, we measured %changeIH_{LC}, a measure that controls for the effects of the force condition on the active sending arm²¹. This measure of inhibition was normal in both arms, indicating that the abnormality we had found previously may be due to interactions between non-paretic arm circuits and local inhibitory circuits affecting the paretic arm. These details should be examined in future studies. Future studies may also be able to expand on whether differences in force level can lead to significant differences in levels of inhibition recruited^{20, 27, 28, 36, 37}.

Clinical Relevance

Despite modest enrollment numbers, the substantial neurophysiologic data obtained in our group of stroke survivors with common neuroanatomical lesion overlap and a range of functional outcomes allowed for a demonstration of a relationship between the primary physiologic measure and upper extremity function. Patients with greater increases in non-paretic to paretic inhibition performed better on the nine-hole-peg-test. Taken with the comparison to healthy controls, this argues for more research into the likely complex dynamics of interhemispheric interactions, and leads us away from the simple model of interhemispheric competition¹¹.

Limitations

The conclusions of this study are limited by the small sample size that we were able to enroll. The findings may be specific to patients with lesions in subcortical white matter similar to ours, and with similar clinical characteristics, rather than being generalizable to the larger population of hemiparetic patients. The small sample size also did not provide the power necessary to determine whether the effect differed between patients with dominant or non-dominant infarcts³⁸, nor did we have a large enough sample of right hemisphere dominant patients to conclude whether pre-morbid dominance influenced the changes in interhemispheric inhibition³⁹. The small sample also did not allow us to investigate whether gender had an influence on the abnormalities of interhemispheric inhibition⁴⁰. All of these issues should be explored in future studies.

Conclusions

Currently, experimental interventions for neurorehabilitation including motor imagery, mirror therapy, bimanual training and non-invasive brain stimulation aim at normalizing the interaction between non-paretic and paretic arms. Some therapies, however, do this under the specific hypothesis that the non-paretic arm over-inhibits the paretic arm. Our findings reveal that producing force with the non-paretic arm does not necessarily over-inhibit the paretic arm, and hence during certain motor behaviors, reducing non-paretic to paretic inhibition may not be indicated. Though limited in generalizability by the small sample size,

these findings have demonstrated that abnormalities in interhemispheric inhibition are dynamically task dependent and have direct implication for the neurorehabilitation of stroke patients^{8–10,27–30}.

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Abbreviations

FCR	flexor carpi radialis
IHI	interhemispheric inhibition
MEP	motor evoked potential
MRI	magnetic resonance imaging
NHPT	nine-hole peg test
SICI	short interval intracortical inhibition
TMS	transcranial magnetic stimulation

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Suppliers

- a. 35-E15A, JR3, Inc., 22 Harter Ave, Woodland, CA, 95776, USA, 1-530-661-3677]
- b. Magstim 200 stimulators with Magstim 200 Double Coils 70mm and 60mm, The Magstim Company Ltd., Spring Gardens, Whitland, Dyfed, Wales, SA34 0HR, UK, 44-1-9942-40798
- c. GE Signa HDxt 3.0T MRI Scanner, GE Healthcare, General Electric Company, 3000 N Grandview Blvd, Waukesha, WI 53188
- d. MRICron Software, Chris Rorden, University of South Carolina, 915 Greene St, Columbia SC 29208
- e. SPM5 Statistical Parametric Mapping Software, University College, London, London, England
- f. Micro1401 II D/A Converter and Signal 5 Software, Cambridge Electronic Design Ltd., Unit 4, Science Park, Milton Road, Cambridge, England, CB4 0FE, UK, 44-0-1223-420488
- g. SAS Proc, SAS Institute Inc., 100 SAS Campus Dr, Cary, NC, 27513-2414, USA, 1-919-677-8000

- h.** Graphpad Prism 5, GraphPad Software, Inc., 2236 Avenida de la Playa, La Jolla, CA, 92037, USA, 1-858-454-5577

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Figure 1. Stroke Lesion Overlap Map

Color map demonstrates the voxels in which stroke lesions overlapped across the enrolled patients overlaid on a template normalized brain. This figure demonstrates that stroke effected corticofugal white matter in all 9 patients.

Figure 2. Non-paretic arm force does not over-inhibit the paretic arm

The diagrams in (A) provide a reference for the graphs in (B), (C), and (D). On the left, all graphs represent data obtained from the paretic arm while the non-paretic arm produced force. In the middle, all graphs represent data obtained from the non-paretic arm while the paretic arm produced force. Finally, on the far right in all graphs, the data from the healthy controls is seen. B) In healthy and in stroke patients producing force with the paretic arm, interhemispheric inhibition (%changeIHI) increases. In stroke patients producing force with the non-paretic arm, interhemispheric inhibition is significantly reduced, demonstrating that there is not an over-inhibition but rather under-inhibition from non-paretic to paretic arms. C) Local inhibition (%changeSICI) is reduced in healthy controls and in the non-paretic arms

of patients producing force with the paretic arm. Local inhibition does not change in the paretic arm, though, when the non-paretic arm produces force. D) Corticospinal excitability (%changeMEP) increases in healthy controls and in the non-paretic arms of stroke patients producing paretic arm force. Excitability, though, doesn't change in the paretic arm when stroke patients produce force with the non-paretic arm. *=statistically significant difference, $p<0.05$.

Figure 3. Inhibition and Hand Function

A robust regression revealed a positive relationship between increasing interhemispheric inhibition (%changeIHI) targeting the paretic arm during non-paretic force and paretic arm performance on the NHPT. The grey point is the outlier identified by the robust regression method.

Table 1

Patient Characteristics

Patient	Gender	Lesion Side	Age	Years Since Ischemic Stroke	NHPT*
1	F	R	67	4	67
2	F	L	80	5	31
3	M	R	58	8	83
4	M	R	47	32	75
5	F	R	63	6	7
6	M	L	53	5	7
7	F	L	64	8	6
8	M	L	61	1	87
9	M	R	72	3	8

All patients were right handed prior to stroke except for patient 6 who was and remained left-handed. Healthy controls were matched to pre-morbid handedness.

* Nine-Hole-Peg-Test,

7 Patient unable to hold pegs

Table 2

Baseline and Matched Measures

CONDITION	MEASURE	PARETIC FCR	NON-PARETIC FCR	DIFFERENCE
Baseline	MVC	7.7 ±1.8 Nm (n=9)	10.5 ±2.3 Nm (n=9)	$t_8=1.275$, $P=0.238$
	Increase in background EMG of resting FCR During 70%MVC Condition of contralateral active FCR	4×10–5 ±45×10–5 mV (n=8)	7×10–5mV ±22×10–5 (n=9)	$t_7=0.06$, $P=0.96$
	rMT (% Maximum Stimulator Output)	59%±3 (n=8)	61%±5 (n=9)	$t_7=0.39$, $P=0.71$
	Baseline MEP Amplitude	274 µV ±87 (33% of maximum amplitude) (n=8)	266 µV ±82 (34% of maximum amplitude) (n=9)	$t_7=0.23$, $P=0.82$
IHI	Starting IHI	68% ±5 (n=7)	70% ±4 (n=8)	$t_6=0.55$, $P=0.60$
	Increase in TS-MEP from 0% to 70%MVC Conditions (Matched by reducing TS-MEP intensity)	9µV ±19 (n=7)	38µV ±9 (n=8)	$t_6=1.44$, $P=0.20$
IHIc	Increase in TS-MEP from 0% to 70%MVC Conditions (Matched by reducing TS-MEP intensity)	38µV ±42 (n=5)	43µV ±40 (n=5)	$t_4=1.97$, $P=0.12$
	Increase in CCS10-MEP from 0% to 70%MVC Conditions (Matched by reducing TS-MEP intensity)	11µV ±32 (n=5)	56µV ±37 (n=5)	$t_4=1.69$, $P=0.17$
SICI	Starting SICI	56% ±6 (n=7)	48% ±4 (n=8)	$t_5=-0.36$, $P=0.74$
	Increase in TS-MEP from 0% to 70%MVC Conditions (Matched by reducing TS-MEP intensity)	8µV ±6 (n=6)	34µV ±21 (n=6)	$t_5=0.67$, $P=0.54$