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Corticospinal Responses of Quadriceps are Abnormally Coupled with Hip Adductors in Chronic Stroke Survivors

Chandramouli Krishnan, PT, PhD^{1,*} and Yasin Dhafer, PhD^{1,2}

¹Sensory Motor Performance Program, Rehabilitation Institute of Chicago, IL, USA

²Department of Biomedical Engineering, Northwestern University, Chicago, IL, USA

Abstract

Stroke survivors often lose the ability to move their joints independently, which results in abnormal movement patterns when attempting to perform an isolated motion. For instance, many stroke subjects exhibit unwanted secondary knee extension movement when performing hip adduction. This study aimed at characterizing whether the neural substrates mediating abnormal activation patterns after stroke are of cortical origin. We developed a novel transcranial magnetic stimulation protocol to evaluate the extent of abnormal across-joint coupling of corticospinal responses in chronic stroke survivors. In stroke survivors, we found that the magnitude of motor evoked potentials of the vastus lateralis and vastus medialis during isometric hip adduction were significantly higher than those recorded during knee extension at similar background activity ($P = 0.03$ & $P = 0.01$). Moreover, motor evoked potential coupling ratios of the quadriceps muscles were significantly different than those observed in healthy controls ($P = 0.005$ to $P = 0.037$). No differences in motor evoked potential coupling ratios were observed between the younger and older adults ($P = 0.474$ to $P = 0.919$). These findings provide evidence for the first time that stroke subjects exhibit abnormal excitability of the quadriceps muscle corticospinal neurons when performing isometric hip adduction. Importantly, the abnormal corticospinal responses observed in stroke subjects were not mediated by aging. The results of this study provide new insights into the mechanisms underlying loss of independent joint control after stroke and have meaningful implications for post-stroke interventions. Moreover, the proposed ‘motor evoked potential coupling ratio’ may serve as an effective probe to evaluate cortical contributions to abnormal muscle synergy after stroke.

Keywords

Stroke; hemiparesis; TMS; synergy; across-joint coupling; lower-extremity; MEP; aging; EMG; tDCS

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*Address for Correspondence: Sensory Motor Performance Program, Suite 1407, 345 E Superior Street, Chicago, IL – 60611, Phone: (312) 238-2992, Fax: (312) 238-2208, c-krishnan@northwestern.edu.

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Introduction

Loss of independent joint control is one of the most common neuromotor impairments that occur after stroke (Brunnstrom, 1970, Twitchell, 1951). The inability to perform movements in an isolated fashion results in the emergence of stereotypical movement patterns involving tight coupling of motions across joints (Cruz and Dhaheer, 2008, Dipietro et al., 2007). This abnormal across-joint coupling has been shown to exist in both upper and lower extremities, irrespective of whether the task is static or dynamic (Cruz and Dhaheer, 2008, Dipietro et al., 2007, Schwerin et al., 2008). Interestingly, these abnormal stereotypical movement/torque patterns are known to correlate with the loss of functional ability in stroke survivors (Cruz et al., 2009). As a result, an understanding of the mechanisms that contribute to abnormal across-joint coupling may assist in identifying appropriate neurophysiological targets for functional recovery in stroke.

While there is compelling evidence for the presence of tight coupling of motions across joints, the mechanisms that mediate such movement patterns remain poorly understood. One possible mechanism may be that the structural reorganization of the brain following stroke can be maladaptive. The structural changes that occur after stroke are often characterized by axonal sprouting of undamaged intracortical and interhemispheric neuronal projections to the damaged regions of the brain (Carmichael, 2003, Carmichael, 2008, Carmichael et al., 2005). Although this plasticity mediates functional recovery, the new neural networks that are established during the process of reorganization may also result in abnormal connections with negative consequences on neuromotor recovery (Beauchamp and Ro, 2008). Moreover, stroke induced physiological alterations, such as increased cortical overlap of joint representations and decreased cortical spatial resolution for recruiting individual muscles, may affect the output properties of the motor cortex in such a way that it may promote abnormal across-joint coupling (Yao et al., 2009, Yao and Dewald, 2006).

It seems reasonable that if the neural substrates of abnormal across-joint coupling are of cortical origin, then the output of the motor cortex (corticospinal responses) when performing a simple isolated task should also be coupled. An observation of such coupled responses will also provide a much stronger evidence for the presence of abnormal neuronal connections in stroke survivors. However, to the best of our knowledge there are no studies that have evaluated whether monohemispheric stroke results in abnormal across-joint coupling of the corticospinal responses. To this end, we examined whether the excitability of the corticospinal neurons of the knee extensor muscle groups when performing an isometric hip adduction task was abnormally modified after stroke. We hypothesized that the stroke subjects would demonstrate abnormal higher corticospinal responses of the quadriceps muscle group during an isometric hip adduction task.

Methods

Subjects

Eight chronic stroke survivors (Age: 55.9 ± 6.6 years, Height: 1.73 ± 0.09 m, Weight: 78.1 ± 14.3 Kg), seven able-bodied young control subjects (Age: 27.3 ± 5.0 years, Height: 1.74 ± 0.04 m, Weight: 67.6 ± 3.5 Kg) and four older adults (Age: 53.3 ± 8.7 years, Height: 1.76 ± 0.02 m, Weight: 76.6 ± 7.9 Kg) participated in this research study. Data from older adults were used to evaluate whether aging contributes to abnormal coupling of the corticospinal responses. Stroke subjects were included in the study if they 1) were between 18 and 70 years of age, 2) had a first ever monohemispheric stroke at least one year prior to participation, 3) had a cortical and/or sub-cortical lesion that was documented by radiologic findings, and 4) had the ability to perform hip adduction and knee extension movements when standing on the non-paretic leg. Exclusion criteria for both the stroke and control

groups included: 1) contraindications for the application of transcranial magnetic stimulation (TMS), 2) a history of seizures and medications known to alter central nervous system excitability, 3) inability to elicit a clearly distinguishable motor evoked response from the thigh muscles, 4) a history of a recent lower-extremity injury, fracture, or surgery, 5) severe osteoporosis or metabolic disorders, and 6) a history of unstable or untreated cardiovascular diseases. All subjects provided written informed consent to participate in the study using a form that was approved by the Northwestern University Human Subjects Research Institutional Review Board.

Transcranial Magnetic Stimulation

TMS elicited motor evoked potentials (MEPs) were recorded from the paretic leg of the stroke survivors and from the dominant leg of the control subjects using surface electromyography. After cleaning the skin over the electrode placement sites with alcohol swabs, surface electromyography (EMG) preamplifiers were placed over the muscle bellies of vastus lateralis, rectus femoris, vastus medialis, and adductor longus. The electrode placement sites were standardized according to the recommendations of Perotto & Delagi (Perotto and Delagi, 1994). A common ground was placed on the skin over the dorsum of the hand. The electrodes were tightly secured to the skin using adhesive tapes and self-adherent elastic Coban wrap (Dynarex Corp., Orangeburg, NY, USA).

The subject was then seated on a chair and a linen cap, which was used to mark the coil position for the lower-extremity hotspot, was tightly secured to the subject's head with head and chin straps. Single-pulse TMS was delivered using a Magstim 200 stimulator (Magstim, Whitland, UK) via a 110 mm diameter double-cone coil. The coil was oriented to induce a posterior-to-anterior current flow in the cortex. The hotspot of the thigh muscles was established over the contralateral motor cortex of the test leg (i.e., ipsilesional motor cortex for stroke subjects and left motor cortex for the control subjects who reported right leg as their kicking/dominant leg) (Madhavan et al., 2011). The hotspot was located by determining the coil position that best elicited an MEP response in both the adductor longus and vastus medialis muscle. The hotspot was, on average, approximately 1 cm posterior and 2.0 cm lateral to the vertex.

Experimental Set-up and Protocol

The subject was tightly secured in a computer-controlled, motorized, instrumented robotic exoskeleton (Hocoma, Zurich, Switzerland) using thigh cuff, shank cuffs, and pelvic straps (Figure 1). The thigh and shank cuffs were instrumented with six-degree-of-freedom load cells to measure the interaction forces/moments between the subject and the exoskeleton. The dimensions of the exoskeleton were adjusted for each patient such that the hip and knee joint centers of the robotic device aligned with those of the subject. The testing leg of the robotic device was then positioned at a posture that resembled closer to the toe-off position during gait and was rigidly secured in this position using custom designed metallic clamps and braces. A body-weight support harness system was used to provide approximately 20% to 25% of body-weight support while the subjects stood on a 3-inch wooden platform that was mounted on a stationery treadmill (Cruz and Dhaher, 2008). The wooden platform was used to ensure that the subject's foot of the testing leg did not touch the ground during the experiment.

The subject was then asked to produce maximum voluntary isometric contractions (MVICs) in two directions (hip adduction and knee extension). The MVICs were performed to obtain maximum torque and muscle activity data for use when setting the target torques and normalizing the EMG data. Loud verbal encouragement and visual feedback of the real-time torque signals were provided during MVICs to facilitate maximal effort. After a two-minute

rest period, the TMS coil was placed over the hotspot location marked on the linen cap and tightly secured to the subject's head using Velcro tapes secured between the coil casing and the top of the linen cap. An additional chin strap was attached to the coil and foam pads were placed between the head and either lateral aspect of the coil to improve the stability of the coil placement. The TMS coil cable was supported using a custom designed overhead pulley system and coil holder stand. The location of the coil position was constantly monitored during the experiment to ensure that the coil position remained the same throughout the experiment.

TMS intensity was adjusted such that the elicited MEPs during a 10% hip adduction MVIC contraction were clear and distinguishable from the background activity (Barthelemy and Nielsen, 2010, Roy and Gorassini, 2008). This intensity was used throughout the experiment. After determining the TMS intensity, the subject was then asked to perform isometric contractions of the hip adductors and knee extensors at various submaximal contraction intensities (10%, 30%, and 50% of maximum) in a random order. Isometric contractions were performed at several contraction intensities in order to perform a *post-hoc* analysis that would minimize the extent to which background EMG activation might affect the amplitude of MEP responses (see data management & analyses for more details). We had the control subjects perform a 5% MVIC contraction as our pilot analysis indicated that matching of background activation between the two directions was more precise when this contraction intensity was included.

The torque required by the subject to generate was displayed one at a time as a circular cursor on a LCD computer monitor placed in front of them. The subject was instructed to match the target torque for 200 ms by placing a circular cursor, which moved in response to the loads applied over the load cell, on the target torque cursor. When the subject was successful in matching the target torque ($\pm 5\%$ of target torque for 200 ms), the TMS device was triggered to deliver a single-pulse using an automated triggering algorithm code written in MATLAB v.7.0.4 (MathWorks, MA, USA). The software also ensured that the TMS device was not triggered if the off-axis deviation due to secondary torques generated at the knee (during hip adduction target-matching) or hip (during knee extension target-matching) joints exceeded by $\pm 5^\circ$. Seven to twelve trials were performed at each load and target direction (hip adduction and knee extension). Adequate rest periods were provided between each subsequent trial to minimize the effect of fatigue.

Data Management & Analyses

Custom software written in MATLAB and LabVIEW v.7.0 (National Instruments Corp., Austin, TX) was used to collect and analyze the TMS data. EMG data were sampled at 1000Hz using two 16 bit A-to-D conversion boards (NI PCI-6031 E and NI PCI-6033E, National Instruments Corp., Austin, TX).

MEP Analyses—In order to analyze the TMS data, an MEP window was established for each muscle in each subject by finding the onset and offset latencies from ensemble averages of MEPs recorded during the target-matching task. A 200 ms window was set prior to the recorded TMS trigger pulses to determine the background EMG activation during target-matching. The root mean square amplitude within the MEP window and pre-stimulus EMG window were used to calculate MEP amplitude and background activity, respectively (van Elswijk et al., 2008). The background activity was subtracted from the MEP amplitude to determine the incremental MEP amplitude during target-matching ($\Delta MEP = [MEP - Background]$) (Schieppati et al., 1996, van Kuijk et al., 2009). The mean incremental MEP amplitude of all the trials at each contraction intensity level was expressed as a percentage of

peak EMG values obtained during the MVIC trials. The mean background activity was also normalized to the peak MVIC values.

It is typical that subjects exhibit higher background EMG activation when the muscles act on the primary direction than on the secondary direction (i.e., higher quadriceps activation during knee extension than during hip adduction). Because the magnitude of background activation affects the amplitude of corticospinal responses (Hess et al., 1986), we performed a *post-hoc* analysis in which we attempted to match the background activation of each muscle in each subject during the two tasks (e.g., background activation of vastus medialis during hip adduction was matched to those recorded during knee extension) (Schieppati et al., 1996). This was easily accomplished with our experimental protocol where subjects performed target-matching at several intensities in both target directions. The contraction intensity at which the muscle activation in the secondary direction (i.e., knee extension while hip adduction and vice versa) was closer to the primary direction was chosen for the analysis. We chose to use this *post-hoc* analysis approach with a torque-matching paradigm rather than having our subjects match EMG targets to ensure similar background activation between the primary and secondary directions because of two reasons: 1) our pilot testing indicated that stroke subjects had greater difficulty in matching EMG targets than torque targets, and 2) because we tested more than one quadriceps muscle, it was nearly impossible for us to have our subjects match the required EMG values in all the three muscles within the same trial.

MEP Coupling Ratio—To determine the extent of across-joint coupling of corticospinal responses for each subject, the difference in the mean MEP amplitudes recorded in the primary and secondary directions was normalized to the sum of the MEP amplitudes obtained from the two directions. For example, the MEP coupling ratio of vastus medialis was calculated as follows:

$$\left[\text{VMMEP}_{\text{coupling ratio}} = \frac{\Delta \text{VMMEP}_{\text{Extension}} - \Delta \text{VMMEP}_{\text{Adduction}}}{\Delta \text{VMMEP}_{\text{Extension}} + \Delta \text{VMMEP}_{\text{Adduction}}} \right].$$

A value greater than ‘zero’ (i.e., positive values) indicates that corticospinal excitability of the vastus medialis was higher in the primary direction (i.e., knee extension) than in the secondary direction (i.e., adduction); whereas a value less than ‘zero’ (i.e., negative values) indicates that the excitability was higher in the secondary direction as compared to the primary direction.

Statistical Analyses

All statistical analyses were performed using SPSS for windows v. 19.0 (SPSS Inc., Chicago, IL, USA). A 2×2 mixed-factor Analysis of Variance (ANOVA) was performed to examine the effect of target direction (hip adduction vs. knee extension) on MEP responses, with group (stroke vs. control) as the between-subjects factor. A Greenhouse-Geisser correction was employed in the statistical analyses when the sphericity assumption was violated. Significant interaction effects were followed by *post-hoc* analysis using paired t-tests to test whether the differences in the MEP amplitudes between target directions varied across groups. Two-sample independent t-tests were used to determine significant differences in MEP coupling ratios between the stroke and the control groups. A significance level of $\alpha = 0.05$ was set for all statistical analyses.

RESULTS

The physical and clinical characteristics of the stroke subjects are provided in Table 1. The mean background activity of the tested muscles were similar between the primary and secondary directions in both the stroke and control subjects ($P = 0.09$ to 0.74), indicating that the trials were adequately matched to minimize the confounding effects of background activation on MEP amplitudes. The MEP responses of the vastus medialis and vastus lateralis muscles recorded during hip adduction were typically larger than those elicited during knee extension in stroke subjects (Figure 2). The 2×2 mixed-factor ANOVA indicated a significant interaction between group and target direction for MEP amplitudes of vastus medialis and vastus lateralis muscles ($P = 0.023$ and $P = 0.016$). *Post-hoc* analysis of the interaction effect revealed that the mean MEP amplitudes of the vastus medialis and vastus lateralis muscles were significantly higher during hip adduction than during knee extension in stroke subjects ($P = 0.03$ and $P = 0.01$, Figure 3), whereas it was not the case for the control subjects ($P = 0.28$ and 0.18 , Figure 3). The MEP coupling ratios of the vastus medialis, vastus lateralis, and rectus femoris were also significantly different between the stroke and the control groups ($P = 0.005$ to $P = 0.037$, Figure 4A).

There were no significant differences in MEP coupling ratios between the young and the older adults ($P = 0.474$ to $P = 0.919$, Figure 4A); however, significant differences in MEP coupling ratios of the quadriceps muscles were observed between the older adults and the stroke subjects ($P = 0.005$ to $P = 0.032$, Figure 4A). There was also no significant relationship between age and quadriceps MEP coupling ratio (average of the MEP coupling ratios of vastus medialis, vastus lateralis, and rectus femoris), indicating that aging had minimal effects on MEP coupling ratios ($P = 0.435$ & $P = 0.706$, Figure 4B).

DISCUSSION

We used a novel TMS paradigm to evaluate whether the corticospinal responses are abnormally coupled across joints in stroke survivors. Our results indicate that the corticospinal excitability of the quadriceps muscles is differentially modified after stroke. Specifically, stroke survivors exhibited higher excitability of the quadriceps muscles when performing a hip adduction task than during a knee extension task, which was contrary to that observed in the control subjects. This response was consistent in all our subjects indicating that the exaggerated across-joint coupling of the corticospinal responses in stroke survivors is not a random finding.

Following stroke, many subjects often lose the ability to control the muscle groups independently (Brunnstrom, 1970, Twitchell, 1951). This loss of independent joint control often results in undesired coupling of joint movements that are inappropriate for the task being performed (Cruz and Dhaheer, 2008, Dewald et al., 1995, Yao et al., 2009). The existing evidence suggests that the neural substrates mediating this abnormal coupling may be of cortical origin (Gerachshenko et al., 2008, Yao et al., 2009). The cortical representations of the upper-extremity muscles in stroke survivors have been shown to overlap to a much larger extent than control subjects (Yao et al., 2009). This increased overlap also correlates with abnormal coactivation patterns and across-joint torque coupling in stroke survivors suggesting that abnormal cortical overlap of muscle representation may be one of the underlying mechanisms that mediate post-stroke loss of independent joint control. Data from existing literature also indicate that stroke subjects exhibit abnormal corticospinal excitability of the upper-extremity muscles that are antagonists to the intended movement (Gerachshenko et al., 2008). This suggests that stroke results in abnormal anatomical or physiological alterations that results in the increased excitability of the non-synergistic muscles that are unnecessary for the intended motion. Our results of abnormal

quadriceps muscle excitability during hip adduction than during knee extension, despite controlling for background activation, further support the presence of altered regulation of corticospinal neuronal excitability in stroke survivors. This altered excitability may promote abnormal behavioral responses, which may in turn lead to the formation of atypical movement patterns such as emergence of abnormal muscle synergies during voluntary movements initiated by stroke survivors. We note that, however, there is insufficient data from the current study to determine whether this altered excitability mediates abnormal knee extensor muscle synergy that is commonly observed after stroke. Further investigation is required to systematically verify the existence of a potential causal relationship between the two.

We expected that the quadriceps muscle corticospinal responses of the stroke subjects would be abnormally high during hip adduction in comparison to the control subjects. However, we did not expect that the excitability of the quadriceps muscle corticospinal neurons during hip adduction would be higher than the excitability observed during knee extension (i.e., negative MEP coupling ratios), which is the muscle's primary direction of action. Our finding of higher corticospinal responses during hip adduction than during knee extension in stroke survivors is a little surprising and counter-intuitive. One possible explanation relates to the differences in the intensity of contractions between the two directions. Due to the well-known effect of background activation on MEP responses (Hess et al., 1986), we intended to match the background EMG activation of each muscle in both the primary and secondary directions. While we were successful in matching the background activation between the two directions, the contraction intensity at which the subjects performed the two tasks with the same background activity differed. The median contraction intensity for the primary target-matching direction, for instance, was 10% of maximum, whereas to generate similar background activation observed in the primary direction the subjects had to perform target-matching at 30% of maximum in the secondary direction (i.e., target-matching at 30% of MVIC generated in hip adduction produced quadriceps activation values that were similar to those observed during 10% of maximum knee extensor contraction). It seems plausible that the net voluntary effort, rather than background activation, is critical in determining the excitability of the motor cortex. If this is the case, then the MEP coupling ratios should be positive when the effort at which the contractions performed in the two directions are matched for. Indeed, the mean MEP coupling ratios were positive for all the muscles (except stroke vastus medialis) in both groups when the motor evoked responses at similar contraction intensities were compared, yet the between-group differences remained (Stroke MEP coupling ratios: -0.04 to 0.16 , Control MEP coupling ratios: 0.16 to 0.59).

What could be the origin of abnormal coupling of corticospinal responses post-stroke? The exact neural mechanisms underlying this abnormal corticospinal excitability are not clear. Based on the existing evidence, we believe that the plasticity of the brain during the recovery process may underlie this phenomenon. Both animal and human studies suggest that recovery after stroke is associated with axonal sprouting in the cortical and subcortical regions adjacent to the lesion site (Carmichael, 2003, Carmichael, 2006, Schaechter et al., 2006). It is possible that such axonal sprouting could have formed aberrant neuronal interconnections between the proximal and distal muscle groups resulting in coupling of responses between the two. The neuroplastic changes mediated by gamma-aminobutyric acid (GABA) neurotransmitters could be another possible mechanism for the observed coupling of the corticospinal responses (Jacobs and Donoghue, 1991, Lazar et al., 2010, Liepert et al., 2000). Evidence suggests that GABAergic pathways are inhibited after stroke (Liepert et al., 2000, Manganotti et al., 2002). Because a reduction in GABA activity promotes expansion of cortical representation and neuronal hyperexcitability through reduced intracortical inhibition, post-stroke inhibition of GABA pathways may have promoted abnormal excitability of adjacent corticospinal neurons, not associated with the

intended movement (Jacobs and Donoghue, 1991, Schiene et al., 1999). Alternatively, abnormal neuronal activity at the spinal level may have contributed to the observed coupling of the corticospinal responses. There is some evidence to suggest the presence of heteronymous stretch reflex facilitation and reflex mediated coupling of lower-extremity muscles following stroke (Finley et al., 2008). However, such coupled reflex responses are selectively seen in biarticular rectus femoris; whereas our findings are more global suggesting that changes at the spinal level alone may not fully explain our results. Nevertheless, further experiments are needed to understand the physiological origin of the MEP abnormality in stroke survivors.

Clinical Implications

The results of this study have potential implications for the way in which noninvasive brain stimulation (NIBS) is applied to promote motor recovery after stroke. There is a growing interest in evaluating the clinical effects of NIBS in stroke population as several studies have shown that NIBS can be effectively used to modulate cortical excitability, enhance motor adaptation and learning, and influence motor memory consolidation (Hunter et al., 2009, Nitsche and Paulus, 2000, Pascual-Leone et al., 1998, Reis et al., 2008). However, our results suggest that NIBS should be applied with caution, especially when targeting lower-extremity recovery. We speculate that simple application of NIBS, such as repetitive-TMS or transcranial direct current stimulation, to up-regulate or down-regulate the excitability of the cortical hemispheres will result in global modulation. Therefore, it is likely that this global enhancement may also result in enhancement of abnormal across-joint coupling of the corticospinal responses, possibly leading to altered behavioral responses and post-stroke dysfunction. While there is some evidence to suggest that non-invasive brain stimulation may actually decouple abnormal synergistic responses in the upper-limb muscles (McCambridge et al., 2011), it is currently not clear whether such an effect can be reliably obtained in lower-extremity muscles, especially considering the fact that the spatial resolution of the lower-extremity cortical representation is poor (i.e., isolated targeting of the lower-extremity muscles is very difficult). We are currently working to evaluate the effect of NIBS on abnormal coupling of the corticospinal responses and the best ways to incorporate NIBS as a therapeutic adjuvant to help mitigate post-stroke functional impairments. Until further evidence is available, we recommend that investigators consider that NIBS may promote abnormal across-joint coupling when used as a therapeutic adjuvant for post-stroke lower-extremity neuromotor recovery.

Potential Limitations

There are some potential limitations in this study. The small sample size of this study limits the ability to generalize our findings to a broader stroke population. However, the observed abnormal MEP coupling ratios were present, albeit in varying levels, in all our stroke subjects irrespective of lesion type and location. This suggests that our findings may be typical in the population of stroke survivors at large. Another concern is that our control group was not age matched to the stroke group. However, there is currently no evidence to suggest that aging induces abnormal neuronal connectivity that would result in altered across-joint torque or corticospinal responses coupling. Indeed, existing evidence indicates that elderly subjects have normal across-joint torque coupling and cortical control mechanisms that suppress unwanted contractions of the muscles that are non-synergistic for the performed action (Cruz and Dhaher, 2008, Gerachshenko et al., 2008, Yao et al., 2009). Moreover, when comparing the data from the young and older adults, it appears that the older subjects behave similar to the younger subjects and showed no signs of abnormal MEP coupling ratios (Figure 4A & 4B). Further, we did not find any correlation between subjects' age and MEP coupling ratio indicating that age was not a confounding factor. Another limitation is that the current study was not designed to evaluate whether the observed

alterations in corticospinal excitability contributes to behavioral abnormality in stroke subjects as we controlled for secondary torque generation in our experimental protocol. As a result, it was not possible to characterize how MEP modulation relates to secondary torque generation and whether the abnormal cortical excitability of the quadriceps muscle group is detrimental to function. However, considering the strong evidence related to the presence of abnormal muscle synergy and the associated across-joint coupling in stroke subjects, it appears that this abnormal neuronal excitability may impair functional performance.

Conclusion

In summary, this is the first study to report that quadriceps muscle corticospinal responses are abnormally coupled with hip adductors in chronic stroke survivors. We observed significantly higher excitability of the quadriceps muscle corticospinal neurons during hip adduction than during knee extension in stroke survivors. The across-joint MEP coupling ratios for the quadriceps muscle were also significantly higher for the stroke survivors in comparison to both the young and older subjects. These findings suggest that there is a dysregulation of cortical inhibitory-excitatory regulatory mechanisms, resulting in abnormal excitability of the lower-extremity muscles that are unwanted for a particular intended motor action. Further work is required to elucidate the mechanisms that mediate abnormal coupling of corticospinal responses and to determine whether the altered corticospinal excitability mediates the emergence of abnormal muscle synergies after stroke.

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Abbreviations

TMS	transcranial magnetic stimulation
MEP	motor evoked potential
EMG	electromyography
MVIC	maximum voluntary isometric contraction

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Figure 1.
Schematic representation of the experimental set-up

Figure 2.

Example of rectified ensemble averaged motor evoked responses recorded during the two tasks (hip adduction & knee extension) in a stroke subject. The red traces indicate responses during hip adduction and the blue traces indicate responses during knee extension. Arrows indicate TMS stimulus onset. Note that the motor evoked potentials of the vastus medialis and vastus lateralis muscles are larger during hip adduction than during knee extension.

Figure 3.

Bar graphs representing mean background activation and the corresponding incremental changes in motor evoked potential of the adductor and quadriceps muscles during isometric hip adduction and knee extension in control (left panel) and stroke subjects (right panel). Asterisks indicate significant differences between the two directions at $\alpha = 0.05$. Error bars represent standard error of the mean. Note that the incremental changes in motor evoked potentials of the vastus medialis and vastus lateralis muscles were significantly higher during hip adduction than during knee extension in stroke subjects. Abbreviations: ADL, adductor longus; VM, vastus medialis; RF, rectus femoris; VL, vastus lateralis.

Figure 4.

(A) Bar graphs representing mean motor evoked potential (MEP) coupling ratios of the adductor and quadriceps muscles in stroke, younger (control), and older subjects. Negative values indicate higher excitability in the secondary direction than in the primary direction. Asterisks indicate significant differences ($P < 0.05$). Error bars represent standard error of the mean. Note that the stroke subjects exhibited MEP coupling ratios of all the quadriceps muscles that were quite distinct and contrasting to those observed in both the younger and older subjects, indicating that the corticospinal excitability of the quadriceps muscles were abnormally modified and coupled in the secondary direction when performing a task in the primary direction. Abbreviations: ADL, adductor longus; VM, vastus medialis; RF, rectus femoris; VL, vastus lateralis. (B) Scatterplot demonstrating the relationship between subjects' age and quadriceps MEP coupling ratios. The quadriceps MEP coupling ratio was calculated by taking the average of the MEP coupling ratios of the VM, RF, and VL muscles. There was no significant relationship between age and quadriceps MEP coupling ratios ($P > 0.05$).

Table 1

Characteristics of the stroke subjects

Patient	Dominant Side	Affected Side	Lesion location	Lesion Type	Sex	Age (Yrs)	Years since stroke	FM Score	Modified Ashworth (HA, KE)
I	Right	Right	Left Basal Ganglia	Hemorrhagic	F	51	2.3	21	0,0
II	Right	Right	Left PLIC; Thalamus; Pallidum; Putamen	Ischaemic	F	57	24.4	21	0,0
III	Right	Right	Left MCA Distribution	Ischaemic	M	45	2.8	32	0,0
IV	Right	Left	Right MCA Distribution	Ischaemic	M	60	2.6	24	1,0
V	Left	Left	Right Basal Ganglia	Hemorrhagic	M	52	4.3	27	0,0
VI	Right	Left	Right Temporal Lobe	Ischaemic	M	54	3.8	25	1,1
VII	Left	Right	Left PLIC, Left Corona Radiata	Ischaemic	F	66	1.3	29	0,0
VIII	Right	Right	Left MCA Distribution	Hemorrhagic	M	57	4.0	23	0,0

PLIC, posterior limb of the internal capsule; MCA, middle cerebral artery; M, male; F, female; Yrs, years; FM score, lower-extremity Fugl-Meyer score (maximum score 34); HA, hip adductors; KE, knee extensors.