Corticospinal tract integrity correlates with knee extensor weakness in chronic stroke survivors

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Abstract

Objective: Muscle weakness develops rapidly after stroke, adversely affecting motor performance, and contributing to reduced functional ability. While the contributions of structural and functional alterations in skeletal muscle to post-stroke weakness have been well described, the relationship between motor pathway integrity, measured using both radiological and electrophysiological techniques, and post-stroke muscle weakness is not clear. This study sought to determine the role of corticospinal tract (CST) integrity on knee extensor weakness in chronic stroke survivors.

Methods: Knee extensor strength and activation testing were performed at 90° of knee flexion using an interpolated triplet technique. CST integrity was evaluated using data obtained from Diffusion Tensor Imaging and transcranial magnetic stimulation.

Results: Recordings in nine stroke subjects indicated substantial knee extensor weakness and activation deficits in the paretic legs of the stroke survivors. Regression analysis revealed that asymmetry in CST integrity was strongly related to between-leg differences in knee strength.

Conclusions: The results of this study suggest a strong link between CST integrity and lower extremity strength, and add to the growing evidence of substantial knee extensor weakness and activation impairments in stroke survivors.

Significance: The findings from this study further our understanding of the anatomical and neurophysiological contributions to motor impairments after stroke, which may benefit clinicians and researchers in the field of stroke rehabilitation.

1. Introduction

Profound motor impairment is a hallmark of most types of stroke. Despite recovery of motor function after the initial insult, residual motor deficits are a common finding in a large proportion of chronic stroke survivors. This impairment often results in an inability to perform routine activities of daily living, leading to long-term disability. Muscle strength is a critical component of motor function, and strength preservation is known to be important for optimal functional performance after stroke.
Evidence indicates that substantial weakness is present in the involved as well as uninvolved limbs of stroke survivors (Andrews and Bohannon, 1995, 2000; Gerrits et al., 2009; Newham and Hsiao, 2001). Several mechanisms, such as disuse atrophy, impaired voluntary activation, and alterations in skeletal muscle structure and composition have been implicated to explain these strength deficits after stroke (Hafer-Macko et al., 2008; Horstman et al., 2008; Klein et al., 2010; Miller et al., 2009; Patten et al., 2004). It is possible that these structural and neurophysiological alterations proposed as underlying mechanisms for muscle weakness may occur secondary to the disruption of corticospinal tract (CST) integrity. As a result, the extent of CST damage may have a significant impact on post-stroke muscle weakness.

Several lines of research indicate that upper limb motor recovery after stroke is strongly related to the extent of CST damage and to the optimal conduction of commands via the corticospinal pathways (Dachy et al., 2003; Hendricks et al., 2003a, 2002; Jang et al., 2010; Pennisi et al., 2002; Stinear et al., 2007; Trompetto et al., 2000). Recent evidence suggests that lower extremity function in stroke survivors may also be related to the physiological integrity of the CST (Hendricks et al., 2003b; Madhavan et al., 2010). Therefore, it is reasonable to hypothesize that stroke survivors with many surviving CST fibers and strong conduction of corticospinal commands would demonstrate relative preservation of muscle strength in the lower extremity. However, experimental data to support this notion are lacking. An understanding of the anatomical and neurophysiological contributions to post-stroke muscle weakness is likely to provide new insights to optimize motor performance after stroke. Our present study was performed to determine the magnitude of knee extensor strength and voluntary activation deficits in chronic stroke survivors and to assess the role of CST integrity (structural and physiological) on muscle weakness.

2. Materials and methods

2.1. Subjects

We studied nine chronic stroke subjects (mean age: 58.3, body mass index: 28.3, lower extremity Fugl-Meyer motor score: 25.0, time since onset of stroke: 10.6 years; Table 1) with radiologically documented ischaemic cortical and/or subcortical lesions. The sample consisted of 6 males and 3 females. Subjects with first-ever monohemispheric stroke at least 2 years prior to participation were recruited for this study. Exclusion criteria included: subjects with contraindications to magnetic resonance imaging (MRI) or to transcranial magnetic stimulation (TMS), a history of seizures and medications known to alter central nervous system excitability, absence of clearly distinguishable motor evoked responses from the vastus lateralis muscle, reports of recent fracture or injury to the lower-extremity, signs of abnormal muscle tone and joint contracture at the knee joint, and inability to perform resisted knee extension without significant pain.

All subjects provided written informed consent to participate using a form approved by the Northwestern University Human Subjects Research Institutional Review Board. All subjects participated in three test sessions: Magnetic Resonance Diffusion Tensor Imaging (DTI) to evaluate the structural integrity of the CST, a TMS experiment to assess the corticospinal conductivity of both the lesioned and non-lesioned motor pathways, and knee extensor strength and activation testing to determine the magnitude of quadriceps strength and activation deficits.

2.2. Diffusion Tensor Imaging

The diffusion tensor images were obtained on a Siemens 3T scanner (Allegra; Siemens Medical Solutions, Malvern, PA, USA) using an echo planar imaging sequence with established image acquisition parameters: repetition time = 4500 ms, echo time = 91 ms, flip angle = 90°, voxel size = 2 mm³, b = 1000 s/mm², and directions = 64 (Madhavan et al., 2010). The motion artifacts and diffusion weighted image distortions in different gradient directions were eddy current corrected using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Diffusion Toolbox (Oxford University, Oxford, UK). The fractional anisotropy (FA) images were derived by fitting the diffusion tensor at each brain voxel in the diffusion data using FDT (FMRIB’s Diffusion Toolbox). A non-linear transformation of the FA images was performed using FMRIB’s non-linear Image registration tool to register the FA images into Montreal Neurological Institute standard space. The FA values were calculated within the posterior limb of the internal capsule (PLIC) for both the affected and unaffected hemispheres by eigenvalue decomposition of the diffusion tensors in each voxel (Pierpaoli et al., 1996). The PLIC was delineated bilaterally, from the level of the anterior commissure to the base of the corona radiata, for each participant with reference to FA RGB images and the MRI Atlas of Human White Matter ( Mori et al., 2005). FA is a scalar value and ranges between zero and one, where higher values indicate better PLIC structural integrity. An index of FA asymmetry was computed using the following formula (Madhavan et al., 2010; Stinear et al., 2007):

\[
FA\text{ asymmetry} = \frac{FA_{\text{unaffected}} - FA_{\text{affected}}}{FA_{\text{unaffected}} + FA_{\text{affected}}}
\]
Although the FA asymmetry index yields a value between −1.0 and +1.0, in a practical situation, this ranges between 0 and 1, where lower values indicate less asymmetry between hemispheres.

2.3. Transcranial magnetic stimulation

TMS elicited motor evoked potentials (MEPs) were recorded bilaterally with the subjects seated comfortably on a chair, with their knees and ankles flexed to 90°. Electromyographic (EMG) data were collected using surface Ag/AgCl electrodes (ConMed Sure-Trace, Utica, NY, USA) that were placed over the muscle bellies of vastus lateralis of both legs. Before placing the electrodes, the skin over the vastus lateralis muscle was shaved and cleaned with alcohol to minimize skin impedance. A common reference electrode was placed on the skin over the right patella. The EMG data were bandpass filtered (10–500 Hz), amplified (×1000), and sampled at 2000 Hz using an AMT-8 amplifier (Bortec Biomedical, Calgary, Canada). A custom program written in SPIKE2 software (Cambridge Electronic Design, Cambridge, UK) was used to trigger the stimulator at 0.25 Hz, and to record the trigger pulses and EMG data.

Single-pulse TMS was delivered using a Magstim 200 stimulator (Magstim, Whitland, UK) via a 110 mm diameter double-cone coil. A linen cap was tied tightly on the subject’s head and the estimated location of the vertex was marked on the cap. The stimulation site was marked ~1 cm posterior and 1.5 cm lateral to the vertex (i.e., laterally offset over the contralateral motor cortex of the test leg) (Madhavan et al., 2010; Madhavan and Stinear, 2010). The double-cone coil was placed on the cap at either of the laterally offset positions where the intersection of the two embedded coils was located over the stimulation site. The coil was oriented to induce a posteriorto-anterior current flow in the cortex. A custom designed coil holder stand was used to support the coil cable and the coil position was maintained manually by an assistant. 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 input–output relationships were established first for the non-paretic leg with the coil placed over the non-lesioned hemisphere. During TMS measurements, subjects were provided with real-time EMG feedback on an oscilloscope to match a target contraction corresponding to ~10% of maximum EMG values measured at the beginning of the experiment. The software that triggered the TMS unit was programmed in such a way that it would not activate the trigger if the muscle activation exceeded or was below the 10% MVC window. Contra-lateral MEPs from the non-paretic vastus lateralis muscle were recorded at TMS intensities corresponding to 30%, 35%, 40%, 45%, 50%, 55%, 60%, and 70% maximum stimulator output to generate a recruitment curve. This procedure was then repeated for the paretic vastus lateralis muscle with the coil now favorably offset over the lesioned hemisphere. Ten MEPs were recorded from each coil position, at each intensity and the average of the ten trials was used in the analysis.

A custom program written in MATLAB was used to analyze and process TMS data. An MEP window was established by finding the onset latencies of contra-lateral large MEPS recorded from the non-lesioned hemisphere. In our experience, the onset latencies of paretic muscle MEPS are typically several milliseconds longer than those recorded from the non-paretic muscles. Therefore, we extended the window by 10 ms to capture increased motoneuron activity resulting from late-arriving volleys for the paretic muscle. A window of identical width was set prior to the TMS trigger pulses to determine background activity. The rectified integrated areas (mV s) within the MEP window and prestimulus EMG window were used to calculate MEP amplitude and background activity, respectively. The mean MEP area (mean of the 10 trials) was expressed as a percentage of mean background activity and plotted against the corresponding stimulus intensity to obtain a subject-specific TMS input–output relationship. The slope of the TMS input–output relationship was derived by fitting a best-fit linear equation. We used a conservative linear fit rather than a Boltzmann fit as we chose not to stimulate at intensities that elicited maximum MEPs, accepting an increased likelihood of not detecting a difference in slope (Madhavan et al., 2010). The slope of the input–output (IO) curve recorded from the paretic leg was expressed as a ratio of that from the non-paretic leg to calculate the between-hemisphere asymmetry in corticospinal excitability of the vastus lateralis motor representation (Eq. (1)).

\[
\text{TMS index} = \frac{\text{IO slope}_{\text{paretic leg}}}{\text{IO slope}_{\text{nonparetic leg}}} \tag{1}
\]

2.4. Knee extensor strength and activation testing

Knee extensor strength and voluntary quadriceps muscle activation were assessed at 90° of knee flexion using an interpolated triplet electrical stimulation technique. In this technique, a strong electrical stimulus is introduced during maximal voluntary isometric contraction (MVIC) with the goal of activating motor units that are either not yet recruited or firing submaximally. Inability to completely activate the muscle will result in torque augmentation with the superimposition of the electrical stimulus. The torque increment associated with the superimposition of electrical stimuli is then used to assess the completeness of voluntary activation (Herbert and Gandevia, 1999; Horstman et al., 2008; Krishnan and Williams, 2009; Merton, 1954). Knee strength and activation testing were performed with subjects seated on an isokinetic dynamometer (Biodex Medical Systems Inc., Shirley, NY, USA) with the electrode on the femur aligned with the axis of the dynamometer. Testing began by having subjects perform several sub-maximal contractions and one 5 s MVIC. The practice trials were provided to familiarize subjects with the testing procedures and to potentiate their quadriceps muscles. Subjects were then familiarized with electrical stimulation by superimposing several sub-maximal electrical stimuli through two self adhesive stimulating electrodes (2.75” × 5.0”, Dura-Stick II, Chattanooga Group, Hixon, TN, USA) applied over the proximal and distal surface of the quadriceps muscles (Place et al., 2010). The electrical stimuli were provided using a constant-voltage muscle and nerve stimulator (Grass S48 with an SIU8T Transformer Stimulus Isolation Unit, Grass Technologies, West Warwick, RI).

After a brief rest period, subjects were instructed to perform knee extensor MVICs by extending maximally against the torque-arm pad of the isokinetic dynamometer for approximately 5 s. A train of 3 electrical pulses (100 Hz, 200 μs pulse duration, 150 V) were superimposed on subjects’ maximal voluntary efforts by visually inspecting the torque curve and triggering the stimulator manually at the time-point perceived to be the peak torque (Jayaraman et al., 2006). A second stimulus with identical electrical characteristics as defined above was superimposed approximately 5 s after the completion of the maximal contraction in order to obtain at-rest potentiated triplet evoked knee extensor torque. Three trials were performed with 2 min of rest between each trial. The trial that produced the highest voluntary torque was used in further analysis. A computer program written in LabVIEW (v. 7.0, National Instruments Corp., Austin, TX, USA) was used to administer the test and record data. The raw analog output signals from the biodex dynamometer were converted into actual torque values (N m) by using calibrated conversion factors provided by the manufacturer that were validated onsite prior to the testing. The electromechanical delay between the stimulus delivery and the actual onset of evoked torque was taken into account when calculating voluntary activation values (Oskouei et al., 2003). The extent of voluntary
quadriceps muscle activation was estimated for each leg using the following formula:

\[
\% \text{Activation} = \left[ 1 - \frac{\text{evoked torque during MVIC}}{\text{evoked torque at rest}} \right] \times 100 \quad (2)
\]

The % voluntary activation was then used to predict the maximal torque generating capacity of the quadriceps muscle from the MVIC values using the following equation:

\[
\text{Maximal torque} = \frac{\text{MVIC}}{\% \text{Activation}} \times 100 \quad (3)
\]

The peak torque value obtained from the paretic leg was expressed as a ratio of the value obtained from the non-paretic leg to determine the extent of between-leg asymmetry in knee extensor strength.

2.5. Data management and analysis

All statistical analyses were performed using SPSS for windows v.17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated for each variable. Paired t-tests were used to assess between-leg asymmetry in knee extensor strength, electrically evoked triplet torque at rest, and voluntary quadriceps muscle activation. A ratio of FA asymmetry to TMS index was used as an indicator of CST integrity (Eq. (4)), in which lower values indicate greater functional integrity of the CST.

\[
\text{CST integrity} = \frac{\text{FA asymmetry}}{\text{TMS slope index}} \quad (4)
\]

For example, a subject who has a FA asymmetry of 0.04 (good structural integrity) and TMS slope index of 0.8 (strong physiological integrity) will have a CST integrity of 0.05, whereas another subject who has a FA asymmetry of 0.2 (poor structural integrity) and TMS slope index of 0.4 (weak physiological integrity) will have a CST integrity of 0.5. To the best of our knowledge, there are no known studies that have assessed the influence of FA asymmetry and corticospinal excitability on lower-extremity muscle weakness. However, examining the results from previous studies that have evaluated the relationships between FA asymmetry, corticospinal excitability, and lower extremity impairment suggest that FA asymmetry and a between-hemisphere asymmetry in corticospinal excitability may be linked to the generation of knee extensor torque in a complex manner (Madhavan et al., 2010; Tang et al., 2010). We therefore assessed associations between knee extensor strength asymmetry and: (1) FA asymmetry; (2) TMS index; and (3) a combined weighted index (CST integrity) where a subject with a moderate FA asymmetry and high TMS index would have a CST integrity index that was lower than the TMS index alone would indicate. The best-fit curve estimation analysis was used to evaluate these associations. The 3D relationship between FA asymmetry, corticomotor excitability asymmetry, and knee extensor strength asymmetry was also evaluated by plotting asymmetry in knee extensor strength as a linear function of FA asymmetry and TMS slope indices. A significance level of α = 0.05 was used.

3. Results

All nine recruited chronic stroke patients participated in all three sessions. The mean FA asymmetry was 0.14 ± 0.12 (range: 0.04–0.39). The mean TMS slope index was 0.50 ± 0.41 (range: 0.05–1.3). A representative sample of FA asymmetry, TMS slope index, and knee extensor weakness is provided in Fig. 1. Paired t-tests revealed that the mean peak knee extensor torque, triplet evoked torque at rest, and percent voluntary activation of the paretic legs were all significantly lower than those recorded from the non-paretic legs (P = 0.009 to P = 0.001, Fig. 2). The paretic leg knee extensor strength was on average 51.8% lower than that of the non-paretic leg. This asymmetry was paralleled by large reductions

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**Fig. 1.** Representative examples from one patient showing (A) Coronal view of diffusion tensors. White matter direction is illustrated with anterior-posterior fibers in green, lateral fibers in red, and superior-inferior fibers in blue (e.g., the corticospinal tracts). Cross hairs are positioned to denote the degeneration of white matter in the posterior limb of internal capsule. This patient had a fractional anisotropy (FA) asymmetry of 0.06. (B) Input-output curves from the non-paretic (red) and paretic (blue) legs recorded during maximum voluntary isometric contractions. The X axis denotes the time in milliseconds (ms) and the Y axis shows the torque in Newton-meters (N m). Arrows indicate the time at which the electrical stimulus was superimposed over the quadriceps muscle. The peak knee extensor torque for the non-paretic leg was 208.8 N m and for the paretic leg was 120.3 N m.

**Fig. 2.** Bar charts representing mean knee extensor peak torque (N m), triplet evoked torque at rest (N m), and voluntary quadriceps muscle activation (%) of the paretic and non-paretic legs. Error bars represent standard error of the mean. Asterisks (*) indicate significance at α = 0.05.
there were significant associations between knee extensor strength asymmetry and (1) FA asymmetry, (2) TMS index, and (3) CST integrity (weighted index). However, the weighted index accounted for more of the variance when regressed with knee extensor torque ratios than either FA asymmetry alone or the TMS index alone. The association between FA asymmetry and knee extensor strength asymmetry was best explained by a negative exponential relationship \( (R^2 = 0.62, P = 0.012) \), whereas that of TMS index and knee extensor strength asymmetry was explained by a linear relationship \( (R^2 = 0.54, P = 0.025) \). The best-fit curve estimation analysis revealed a significant negative exponential relationship between CST integrity and knee extensor strength asymmetry (Strength asymmetry = \( 0.68e^{-0.89\text{CST integrity}} \), \( R^2 = 0.76, P = 0.002 \); Fig. 3A). There was also a strong linear relationship when asymmetry in knee strength was plotted as a function of FA asymmetry and TMS slope indices (Strength asymmetry = \( 0.45 – 0.88 \times \text{FA asymmetry} + 0.30 \times \text{TMS index} \), \( R^2 = 0.81, P = 0.007 \); Fig. 3B). The weighted index produced predicted between-leg asymmetry in knee strength values that were similar and strongly correlated \( (R^2 = 0.81) \) to those obtained from a linear combination of FA asymmetry and TMS slope index.

4. Discussion

Knee extensor weakness is a common finding in people with stroke (Bohannon, 2007; Patten et al., 2004). Many authors have attributed this weakness to several factors, such as quadriceps muscle atrophy, alterations in metabolic composition of the quadriceps muscle, and disruption in the volitional capacity to generate maximal muscle force (i.e., quadriceps activation deficits) (Hafer-Macko et al., 2008; Patten et al., 2004). While the muscular and neural components of muscle weakness have been studied earlier, the anatomical and neurophysiological factors that underlie post-stroke muscle weakness remain poorly understood at the level of motor pathway structure and conductivity. Our present study attempts to fill this gap. To the best of our knowledge, this is the first study to evaluate the role of CST on lower-extremity muscle weakness. The findings from this study indicate that both structural and physiological integrity of the CST play a key role on the post-stroke knee extensor weakness. The results of this study further our understanding of mechanisms underlying post-stroke weakness and provide important information that may benefit clinicians when designing rehabilitation interventions to counteract muscle weakness and associated functional performance.

The extent of CST damage has been shown to predict clinical improvements after stroke (Stinear et al., 2007). Additional evidence suggests that the physiological integrity of the corticospinal tract positively affects lower extremity motor performance in chronic stroke survivors (Madhavan et al., 2010). The finding of strong association between CST integrity and knee extensor strength further corroborates that DTI data and TMS derived corticospinal tract excitability measures provide clinically useful information and suggests that these methods have the potential to be used as adjunct tools to evaluate motor performance, monitor patient progression, establish therapeutic goals, and to construct rehabilitation algorithms after stroke.

The results of this study may also have clinically meaningful implications. One of the goals of stroke rehabilitation is to regain strength and control of the affected side. A large proportion of conventional physical stroke rehabilitation occurs during the acute/sub-acute phase, a time period during which the potential for structural and functional reorganization of the brain may be at its best (Biermasz et al., 2004). We believe that rehabilitation after stroke can be individualized (i.e., subject-specific) based on CST integrity. For example, conventionally used resistance training programs may be sufficient to induce sizable gains in muscle strength for subjects with good CST integrity. In contrast, subjects with poorer CST integrity may require addition of other motor priming modalities, such as repetitive TMS or transcranial direct current stimulation, apart from the traditional rehabilitation approaches in order to visualize significant strength gains.

We note that while there is some preliminary evidence to suggest that non-invasive brain stimulation (NIBS) may be a valuable therapeutic adjuvant in people with severe hemiparesis (Boggio et al., 2006; Hesse et al., 2007; Mally and Dinya, 2008), the role of NIBS of the lesioned hemisphere on motor recovery may be limited for severely affected chronic stroke survivors, especially when both the structural and physiological integrity of the CST are severely disrupted (Stinear et al., 2007). These candidates may benefit by priming the non-lesioned hemisphere as it may be the only viable resource left for functional recovery (Stinear et al., 2007). It is to be acknowledged, however, that we do not know if CST integrity measured early after stroke can be correlated systemati-
cally with subsequent lower-extremity muscle performance, since the present study was not designed to investigate the capability of using tract integrity to predict subsequent motor performance. Such an analysis would require a longitudinal study in acute stroke survivors and is beyond the scope of the present study.

A number of researchers have explored the relation between CST integrity and motor performance after stroke, by studying the physiological dysfunction of the motor pathways using TMS-based corticotoric excitability measures (Escudero et al., 1998; Heald et al., 1993; Hendricks et al., 1997; van Kuijk et al., 2009). Others have examined this relationship by studying the anatomical/morphological damage to the CST as estimated using DTI (Cho et al., 2007; Jang et al., 2010, 2005; Madhavan et al., 2010). However, to date, very few researchers have incorporated both TMS-based excitability measures and DTI-based FA measures to study motor outcomes after stroke and these have been limited to upper extremity function (Jang et al., 2010; Stinear et al., 2007). Ours is the first study to investigate mechanisms underlying post-stroke muscle weakness using integrative approaches that simultaneously combined two unique evaluation tools known to have different advantages in predicting motor outcomes (Jang et al., 2010). We found that both FA asymmetry and between-hemisphere asymmetry in corticospinal excitability correlated significantly with knee extensor weakness. However, using a weighted index that accounted for both anatomical and physiological integrity of the CST, we could explain an even larger proportion of variations in knee extensor strength when compared to either FA asymmetry or TMS index alone. This indicates that the mechanisms related to force production in proximal leg muscles are likely not simply related to surviving anatomical or physiological resources alone, but are due to complex interactions between the two. The results of this study also indicate that the ratio of FA asymmetry to TMS index appears to capture much of the variance that is not explained by FA asymmetry or TMS index alone, suggesting that the weighted index may be a useful metric to quantify corticospinal tract integrity for future studies.

A substantial reduction (~52%) in knee extensor strength of the paretic leg in comparison to the non-paretic leg was observed. This strength reduction was paralleled by large reductions in electrically evoked triplet torque at rest (~26%) and by reductions in voluntary quadriceps muscle activation (~28%) indicating that post-stroke quadriceps weakness of the paretic legs involves both neural and muscular impairments. These findings are in agreement with earlier reports that have evaluated knee extensor weakness in acute and sub-acute stroke subjects (Harris et al., 2001; Horstman et al., 2008), but are contrary to those observed in dorsiflexor and plantarflexor muscle groups where post-stroke muscle weakness appears to be mostly related to voluntary activation failure with little contribution from structural muscle changes (Klein et al., 2010; Landau and Sahrmann, 2002). The observed differences in the relative contribution of muscular and neural factors to post-stroke weakness between the thigh and leg muscle groups suggest that quadriceps muscle group is more susceptible than ankle plantar or dorsiflexors to structural alterations after stroke.

Weakness of the “non-paretic” leg is a common finding in majority of stroke survivors (Andrews and Bohannon, 1995, 2000; Horstman et al., 2008). Such weakness has been shown to occur rapidly after the initial neurological insult (~48 h) and is known to persist for at least 3–6 months after stroke (Harris et al., 2001; Horstman et al., 2008). The present study extends these findings further by showing that the “non-paretic leg” may remain weak even years after the stroke. Although the present study did not include a control group to compare strength data of the non-paretic leg, the findings of bilateral activation deficits (~18% on the non-paretic leg) indeed support the presence of non-paretic leg weakness in our sample. This study has some limitations that are worth discussing. We used the quadriceps muscle as our study model. This is for several reasons:

1. The quadriceps muscle group is one of the most extensively studied lower-extremity muscle groups in a wide variety of subject populations including stroke (able-bodied, SCI, Stroke, Osteoarthritis, etc.), which makes it easier to compare our study results with those of others (Gerrits et al., 2009; Harris et al., 2001; Krishnan and Williams, 2010a; Miller et al., 2009; Pang and Eng, 2008; Pang et al., 2005).

2. Quadriceps muscle strength preservation has been strongly linked to functional performance after stroke (Eriksrud and Bohannon, 2003; Gerrits et al., 2009; Horstman et al., 2008; Lomaglio and Eng, 2005; Pang and Eng, 2008), and

3. The reliability of the estimates of voluntary quadriceps muscle activation and motor evoked potentials of the vastus lateralis muscle has been well established in the literature (Norregaard et al., 1997; Wheaton et al., 2009; Zech et al., 2008).

However, because we tested only the quadriceps muscle group, it is not clear whether the correlation observed between CST integrity and muscle weakness is specific to the knee extensors or general to each of the paretic muscles. Therefore, generalizing the results observed to the muscles other than quadriceps muscle group warrants caution and is premature until further evidence is available.

Another limitation is that although corticospinal excitability was assessed on a muscle that represents knee extensor group, FA values calculated within the PLIC cannot be specific to the knee extensors. Therefore, some amount of error may be inherent in our model prediction, although evidence indicates that post-stroke weakness observed in one muscle correlates significantly with other muscles (Bohannon and Andrews, 1998). Also, our study involved subjects with mild-or-moderate to marked but not severe impairments (Sanford et al., 1993). It is possible that people with severe impairments may belong to a different cohort and not show a similar response to those observed in our current sample. Therefore, we recommend caution when extrapolating the results observed from this small sample of carefully selected chronic stroke survivors to the population of stroke survivors at large.

Another concern might be that ipsilateral projections from the non-lesioned hemisphere could have contributed to the strength of the paretic leg. Since ipsilateral connections to the paretic side were not measured in this study, we were unable to quantify the extent to which non-lesioned hemisphere contributed to the measured strength and activation of the paretic leg. In addition, the stimulator used in activation testing was triggered manually by visually inspecting the torque curves. Although we had an experienced tester performing this, the precision of stimulus delivery timing at or near peak torque is inferior to automated torque triggering approach (Krishnan et al., 2009). As a result, it is possible that our approach may have slightly overestimated the magnitude of activation deficits observed in our study sample. Last, this is a cross-sectional study with a small cohort of chronic stroke survivors. As a result, we were unable to characterize whether early incorporation of neurophysiological and imaging measures, such as TMS and DTI, will be helpful in designing patient-specific rehabilitation approaches to improve muscle strength after stroke. Future studies should examine whether measures of CST integrity can be reliably used to identify potential candidates that may benefit specific rehabilitation interventions and also to predict subsequent recovery in muscle strength.

In conclusion, this study potentially provides an understanding of the mechanisms underlying post-stroke muscle weakness at the structural level of motor pathways. The results of this study indicate that both structural and physiological integrity of the CST...
are important for optimal quadriceps strength after stroke. We found significant voluntary activation deficits in both the parietic and the non-parietic legs indicating that bilateral neural impairments that are commonly reported early after stroke do not recover and persist years after stroke. The findings of this study have meaningful implications to clinicians and researchers who focus on improving muscle performance after stroke.

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