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Atypical cortical drive during activation of the paretic and nonparetic tibialis anterior is related to gait deficits in chronic stroke

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Abstract

Objective—The role of cortical drive in stroke recovery for the lower extremity remains ambiguous. The purpose of this study was to investigate the relationship between cortical drive and gait speed in a group of stroke survivors.

Methods—Eighteen individuals with stroke were dichotomized into fast or slow walking groups. Transcranial magnetic stimulation (TMS) was used to collect motor evoked potentials (MEPs) from the tibialis anterior of each lower extremity during rest, paretic muscle contractions, and nonparetic muscle contractions. An asymmetry-index (AI) was calculated using motor thresholds and compared between groups. The average MEP of the paretic leg during TMS at maximal intensity (MEP₁₀₀) for each condition was compared within and between groups.

Results—A significant positive correlation was found between AI and walking speed. Slow-walkers had greater MEP₁₀₀s during the nonparetic contraction than during the paretic contraction or rest conditions. In contrast, fast-walkers had greatest MEP₁₀₀s during the paretic contraction.

Conclusions—Alterations in the balance of corticomotor excitability occur in the lower extremity of individuals with poor motor recovery post-stroke. This atypical cortical drive is dependent on activation of the unaffected hemisphere and contraction of the nonparetic leg.

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Conflicts of Interest

Authors have no conflicts of interest to disclose.

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Significance—Understanding mechanisms underlying function can help to identify specific patient deficits that impair function.

Keywords

Stroke; gait; transcranial magnetic stimulation; asymmetry; lower extremity

Introduction

Following a neurological injury, recovery of lower extremity control and the ability to walk is a primary goal of stroke patients (Bohannon et al. 1991). However, many individuals are left with long term disability of functional ambulation following stroke, despite current standard rehabilitation (Bohannon et al. 1991). Gains in neuroscience research over the last several decades have enhanced our understanding of structural changes in the brain that may underlie functional disability following stroke (Kleim and Jones 2008). Studies have demonstrated the “adaptive capacity” of the central nervous system and the striking ability of neurons to modify structure and function in response to environmental stimuli (Kleim and Jones 2008; Adkins et al. 2004; Jones et al. 1996). However, there remains a large gap in our current understanding of this neuroplasticity and neurophysiologic mechanisms that affect functional recovery in humans post-stroke. Indeed, this lack of understanding has limited our ability to develop effective neurorehabilitation treatments for recovery of motor function (Kleim and Jones 2008; Harris-Love 2013).

Over the past decade, studies using transcranial magnetic stimulation (TMS) to investigate changes in corticomotor excitability following stroke have offered valuable insight into mechanisms for functional recovery of the upper extremity (Harris-Love 2013). Research has found long-term mechanisms of repair and recovery in the brain are associated with varying degrees of functional motor recovery (Harris-Love 2013; Hendricks et al. 2002). Following stroke, TMS measures of decreased corticomotor excitability in the paretic upper extremity during stimulation of the *lesioned* (*contralateral*) hemisphere are associated with poor motor recovery (Trompetto et al. 2000; Butler and Wolf 2007; van Kuijk et al. 2009) and increased excitability is associated with good functional recovery (Butler and Wolf 2007; Dimyan and Cohen 2009; Hendricks et al. 2002). Conversely, paretic motor responses during stimulation of the *nonlesioned* (*ipsilateral*) hemisphere are related to poor recovery (Murase et al. 2004; Turton et al. 1996). These results have created a neurophysiologic model of decreased excitability and increased inhibition of the lesioned hemisphere coupled with hyperexcitability and disinhibition of the nonlesioned hemisphere in those with poor upper extremity recovery (Trompetto et al. 2000; Turton et al. 1996; Butler and Wolf 2007). The relationship of this atypical cortical balance can be quantified (Brouwer et al. 2001; Cicinelli et al. 2003) and has been shown to behave differently during motor function than during rest in stroke (Murase et al. 2004). Studies utilizing new rehabilitation techniques for the upper extremity taking advantage of these mechanisms of cortical neuroplasticity have enabled individuals to reach new gains in functional recovery beyond those made with standard rehabilitation (Orihuela-Espina et al. 2013; Kuhnke et al. 2008).

Despite our growing knowledge of changes in cortical remodeling that occurs for the upper extremity, our understanding of these functional recovery mechanisms in the lower extremity is limited. New technologies in TMS have helped to overcome previous limitations in our ability to target muscle representations of the lower extremity that are located more deeply within the primary motor cortex (Cacchio et al. 2011). Although there are differences between the upper and lower extremity motor organization and control such as anatomical locations of motor maps and lack of fine motor task performance, it is well-established that the motor cortex is actively and intricately involved in lower extremity function such as ambulation (Schubert et al. 1997). Evolving research has indicated that cortical remodeling could behave in a similar pattern to that of the upper extremity, with increased excitability to the paretic leg from the lesioned hemisphere being related to good functional recovery of independent transfers (Hendricks et al. 2003) walking and stair climbing (Steube et al. 2001). There is little evidence on the role of hemispheric balance in lower extremity functional recovery. Madhavan et al. found stronger conductivity from the nonlesioned hemisphere to the paretic ankle muscles was related to poor performance accuracy during an antiphasic ankle tracking task (Madhavan et al. 2010). Still, other studies have found that ipsilateral projections from the nonlesioned hemisphere are essential to functional motor recovery of behaviors involving less cortical input (Hamdy et al. 1998; Muellbacher et al. 1999). Lack of research combined with our inability to reconcile the basis for conflicting results of these studies has limited our understanding of the possible mechanisms underlying motor recovery of functional behaviors such as ambulation, which involve less cortical input than upper extremity behaviors such as reaching and grasping (Schubert et al. 1997).

Another factor that has been shown to influence motor performance of paretic extremities post-stroke is in-phase activation of homologous muscles of the nonparetic contralateral extremity. Greater performance in paretic arm movements have been observed when they are performed in-phase simultaneously with the nonparetic arm than when they are performed with the paretic arm in isolation (Cunningham et al. 2002; Harris-Love et al. 2005; Rose and Winstein 2005). Additionally, individuals post-stroke often demonstrate involuntary symmetric movements of the paretic limb during effortful nonparetic limb movement (Mayston et al. 1999; Nelles et al. 1998). Likewise in the lower extremity, paretic motor performance improves during bilateral in-phasic tasks (Kautz and Patten 2005; Kautz et al. 2006). Tseng and Morton demonstrated that muscle activation patterns in the paretic dorsi- and plantarflexors that were related to kinematic performance showed the greatest abnormalities during anti-phasic bilateral ankle motor tasks (Tseng and Morton 2010). Together, these findings suggest that muscle activation of the nonparetic limb affects the motor behavior of the paretic limb, likely through corticospinal system projections (Tseng and Morton 2010). If such maladaptive corticospinal projections were active during gait, a motor behavior requiring anti-phasic bilateral lower extremity motor coordination, then this could contribute to functional walking deficits in individuals post-stroke. However, no studies to date have directly investigated the differential effect of muscle activation within the paretic and nonparetic limbs on corticomotor input to the lower extremity.

Mechanisms responsible for functional recovery of the lower extremity in stroke are unclear, therefore limiting the ability of rehabilitation specialists to target deficits impairing lower

extremity function such as gait. An understanding of cortical substrates that underlie recovery of motor behaviors during differential activation of the paretic and nonparetic limb involved in walking may explain why some patients respond well to rehabilitation interventions such as gait training while others may never regain adequate motor function for safe community ambulation (Perry et al. 1995). The purpose of this study was to investigate 1) the relationship between measures of cortical inter-limb asymmetry and gait speed and 2) the differences in corticomotor excitability of the paretic leg during resting and active conditions of each leg.

Methods

A case-control design was used. Independent variables were group (fast-walkers or slow-walkers) and condition of contraction (paretic, nonparetic, rest). Dependent variables were motor threshold, asymmetry index (AI) and mean peak-to-peak MEP amplitude at 100% stimulator intensity (MEP₁₀₀) measured with TMS. The study population included 18 individuals (13 males, mean age 61.3±8.3 years, mean time since stroke 57±65 mo.) with chronic stroke (>6 mo.) recruited from local physical therapy clinics and senior centers (Table 1). These values represent mean and standard deviation. The experimental protocol was approved by the University of Delaware IRB and all participants gave written informed consent. All participants sustained a single cortical or subcortical stroke and were able to walk a distance of >10 meters without assistance of another person. Exclusion criteria included more than 1 previous stroke, cerebellar involvement, pain in the lower extremities at rest or during walking, presence of any neurologic conditions other than stroke, and any unsafe TMS testing criteria (Rossi et al. 2009). Participants performed a 10-meter walk test to quantify self-selected walking speeds (Perry et al. 1995). As previous research has established a self-selected walking speed 0.8 m/s is necessary for unrestricted community ambulation in the strokepatient population (Perry et al. 1995), participants were dichotomized into a slow-walking (<0.8m/s) and fast-walking group (>0.8m/s).

Assessment of Cortical Excitability

Participants donned an elastic cap and were comfortably seated upright in an arm chair with knee and ankle angles positioned at 90 degrees with both feet resting on the floor for testing. Double differential surface electrodes with integrated ground (BL-AE, B&L Engineering, Santa Ana, CA) were positioned and secured to the skin over the tibialis anterior (TA) muscles bilaterally. EMG activity was recorded bilaterally and simultaneously using a 6 channel active EMG system (BL-EMG-6, B&L Engineering, Santa Ana, CA) and sampled at a rate of 2000Hz with a 330 gain set on a 16 bit data acquisition board (National Instruments NI USB-6341). The experimenter identified the vertex of the skull and began with the midpoint of the coil aligned antero-posteriorly to the vertex and the coil positioned at the midline of the vertex and 1cm anterior to the frontal midline (Devanne et al. 1997). Custom LabVIEW software (National Instruments, Austin, TX) was developed and used to set intensities, trigger the TMS pulses, and collect EMG data.

Participants were asked to dorsiflex and maintain a light contraction at 15% of their maximal EMG activity during stimulation while searching for the optimal location for

eliciting a MEP of maximal peak-to-peak amplitude (Needle et al. 2013). Magnetic pulses were delivered with a magnetic stimulator (Magstim 200, MagStim Ltd, Wales, UK) through a batwing coil (each wing 11cm in diameter) beginning at 10% stimulator output intensity and gradually increasing to the intensity where a MEP was visibly observed on real-time EMG in the TA of the targeted muscle (Needle et al. 2013). The coil was moved over the scalp as magnetic stimuli of suprathreshold intensity were delivered and the optimal location for eliciting a MEP of maximal peak-to-peak amplitude was found. Optimal locations for both the paretic and nonparetic TAs during facilitation were consistently found to be located on the contralateral side of the vertex of the targeted muscle in all participants *during contraction of the targeted muscle*. The coil positions were carefully marked on the head and used for all recordings. TMS pulses were applied at a rate of 0.2 Hz ranging from subthreshold through 100% stimulator output at intervals of 3 percent of the stimulator's output. Three pulses at each intensity were delivered in random order to the optimal location (Needle et al. 2013). Approximately 60 MEPs were collected for each trial. Three conditions were tested: resting, paretic TA contraction, and nonparetic TA contraction. During the first trial for each leg, participants were asked to keep both legs completely relaxed for the resting condition. For the paretic contraction and nonparetic contraction conditions participants were asked to dorsiflex only the leg being targeted to 15% of their maximum EMG activity throughout the trial, while keeping the other leg relaxed. The order of the testing leg was randomized. Real-time EMG biofeedback was provided to assist participants in maintaining a constant level of muscle activity. If participants were unable to produce a voluntary motor contraction of the paretic TA, they were asked to maintain an effort that produced an observable increase in EMG that they could maintain for 3–4 minutes throughout the trial. All participants were able to produce an observable increase in volitional EMG for both paretic and nonparetic legs. During post-processing, we quantified the precontraction EMG activity for all conditions to determine that all conditions were met. The root-mean squared of the background EMG of the paretic TA for each condition was calculated during a 100ms window prior to the stimulus artifact for each MEP. EMG was recorded bilaterally and simultaneously during all testing conditions. Testing procedures were repeated twice and for each leg.

The maximal response to peripheral nerve stimulation ($M_{\max}$) was collected and used for normalization of MEP amplitude for all data. The common peroneal nerve was located through palpation and confirmed with muscle response of the TA to peripheral nerve stimulation at the level of the fibular head. Nerve stimulation was delivered using a custom electrical stimulator (U-DEL, Newark, DE) while subjects remained seated comfortably in a chair and were asked to relax, with relaxation confirmed with EMG observation. Stimulation was delivered to the nerve with a custom UDEL stimulator using 1ms square electrical pulses of gradually increasing intensities, with 10 seconds between each pulse. The stimulus intensity was increased until no increase in the Mwave was observed with increasing intensity for the TA muscle.

Data Reduction and Analysis

Normalized peak-to-peak amplitudes of the MEPs were plotted against the stimulator output intensity to form a stimulus-response curve (Figure 1). A Levenberg-Marquardt algorithm

was used to fit a modified Boltzmann equation to the data using the following equation (Devanne et al. 1997):

$$y = MEP_{min} + \frac{MEP_{max} - MEP_{min}}{1 + e^{m(I_{50} - x)}}$$

Parameters of minimum MEP (MEP_{min}), maximum MEP (MEP_{max}), slope (m), and intensity at which the curve's slope was the steepest (I_{50}) were derived from the equation. The motor threshold (MT) was defined as the intensity of the curve at which the first derivative increased above 5% of its maximum (Needle et al. 2013). Data were excluded if the stimulus-response curve did not have a R^2 value of greater than or equal to 0.75 (Needle et al. 2013). For each condition, the trial with the highest R^2 value was used for analysis.

We calculated an asymmetry index (AI) by comparing MTs of the paretic and nonparetic TA muscles during the nonparetic contraction condition for all participants. We only calculated AIs during the nonparetic contraction condition because S-R curves of the paretic TA during the paretic contraction and resting conditions did not show good reliability (see results section). Asymmetry indices (AIs) were calculated during stimulation of the nonlesioned hemisphere targeting the nonparetic TA using the following equation (Brouwer et al. 2001):

$$AI = \frac{MT_{paretic} - MT_{nonparetic}}{MT_{paretic} + MT_{nonparetic}}$$

Based on this equation, a positive AI indicates that the contralateral nonparetic TA has *greater* excitability than the ipsilateral paretic TA and a negative AI indicates the contralateral nonparetic TA has *less* excitability than the ipsilateral paretic TA (Brouwer et al. 2001; Needle et al. 2013). AI differences between groups were tested using a t-test. The relationship between AI and gait speed for the entire group was tested using a Pearson product-moment correlation coefficient. An alpha level was set *a priori* at 0.05.

MEP_{100} s were calculated to determine the corticomotor excitability of the paretic leg across conditions, and changes in corticomotor excitability were compared between groups. An average of three peak-to-peak MEP amplitudes of the paretic TA at 100% stimulator output intensity (MEP_{100}) were taken for each condition (paretic TA contracted, nonparetic TA contracted, and resting) (Kim et al. 2004; Harris-Love et al. 2011). An average of three MEPs at 100% stimulator output intensity has previously been used to quantify cortical excitability (Kim et al. 2004). We quantitatively determined the reliability of an average of 3 MEPs at 100% stimulator output intensity for the MEP_{100} measure by calculating intraclass correlation coefficients [ICC 3, k]. SPSS statistical software was used to perform all analysis.

Results

Optimal coil positions were found at 2.0 ± 0.6 cm lateral and 2.2 ± 0.7 cm anterior for the paretic TA and 2.2 ± 0.5 cm lateral and 2.3 ± 0.6 cm anterior for the nonparetic TA. There was

no difference between coil position between subject groups for the paretic TA (anterior, $p = .79$; lateral, $p = .84$) and the nonparetic TA (anterior, $p = .71$; lateral, $p = .86$). We calculated AIs using MTs for all 18 subjects to determine relative corticomotor excitability of each leg during the nonparetic TA contraction condition. During the nonparetic TA contraction, reliable stimulus-response curves were obtained for all subjects for both the paretic and nonparetic TA muscles. During the paretic TA contraction and resting conditions we were unable to obtain consistent and reliable stimulus-response curves from the paretic TA of 5 out of 8 individuals in the slow group. Thus, to compare corticomotor excitability across all conditions, we calculated the MEP₁₀₀ of the paretic leg during all three conditions.

Significant differences were observed between AIs of fast-walkers (0.167 ± 0.077) versus slow-walkers (-0.231 ± 0.161) during the nonparetic TA contraction ($t_{17} = 6.93$, $p < .01$) (Figure 2). All fast-walkers had positive AI values, which is similar to AIs seen when testing able-bodied individuals (able-bodied AI = 0.218 ± 0.18 , $n=12$) (Palmer et al. 2012). A significant positive correlation was observed between AI and walking speed ($r = 0.86$, $p < .01$) (Figure 2). Throughout the nonparetic contraction trial precontraction EMG activation levels of the paretic TA were similar to that of the resting condition for both fast ($6.49 \pm 5.07 \mu V$), and slow ($4.98 \pm 3.09 \mu V$) groups. Precontraction EMG activity in the nonparetic TA during the nonparetic contraction condition was greater than that of the resting condition by at least 2.5 standard deviations for both the fast ($25.01 \pm 10.91 \mu V$) and slow ($17.55 \pm 6.84 \mu V$) groups.

The MEP₁₀₀ measure showed good reliability within individuals ($ICC_{3,k} = 0.962$). Appropriate EMG activity levels within the paretic leg for each condition were met by all participants in the fast (paretic contraction = $28.54 \pm 20.02 \mu V$, nonparetic contraction = $6.36 \pm 5.16 \mu V$, resting = $6.94 \pm 5.81 \mu V$) and slow (paretic contraction = $16.22 \pm 9.73 \mu V$, nonparetic contraction = $5.54 \pm 2.01 \mu V$, resting = $4.37 \pm 1.77 \mu V$) groups. All MEP₁₀₀ data met the assumptions of normality, sphericity, and heteroscedasticity.

A 2×3 mixed design analysis of variance was used to test if groups (fast or slow walkers) differed between conditions (resting, paretic contraction, nonparetic contraction) for the MEP₁₀₀ (Figure 3). There was a significant group by condition effect for MEP₁₀₀ ($F_{2,32} = 10.53$) ($p < .01$). Post-hoc pairwise comparisons were performed using a Bonferroni method. For fast walkers, MEP₁₀₀s during the paretic contraction (0.418 ± 0.242) were significantly higher than resting ($.223 \pm .251$) ($p < .01$) and nonparetic contraction conditions (0.292 ± 0.258) ($p < .01$) (Figure 4). There was no difference between MEP₁₀₀ during the resting and the nonparetic contraction condition ($p = .157$). A different pattern was observed for slow walkers. There was no difference between MEP₁₀₀ during the paretic contraction (0.140 ± 0.170) and the resting condition (0.134 ± 0.189) ($p = .873$). Slow walkers had significantly greater MEP₁₀₀s between nonparetic (0.274 ± 0.244) versus paretic ($p < .01$) contraction. They also had significantly greater MEP₁₀₀s during the nonparetic contraction than the resting condition ($p = .01$) (Figure 4). Patterns in changes in P TA MEP₁₀₀ between paretic and nonparetic contraction conditions were different between fast vs. slow walkers; all fast walkers showed an increase in P TA MEP₁₀₀ from nonparetic contraction during paretic contraction while all slow walkers showed a decrease in P TA MEP₁₀₀ from nonparetic contraction during paretic contraction (Figure 5).

The main effects of group and condition were also significant. MEP₁₀₀ was significantly greater in the fast walkers ($F = 20.52, p < .01$) compared to the slow walkers ($F = 5.41, p = .02$). Between-group pairwise comparisons revealed that MEP₁₀₀ during the paretic contraction was different between groups ($F_{1,16} = 7.53, p = .01$). There was no difference in MEP₁₀₀ between groups for the resting ($F_{1,16} = 0.69, p = .417$) or nonparetic contraction condition ($F_{1,16} = 0.02, p = .878$).

Discussion

The current study provides novel evidence that impairments in cortical drive are related to the self-selected walking speed of individuals with chronic stroke. We observed substantial differences between fast versus slow walkers in cortical AI measures and in MEP₁₀₀ response under each of the three conditions. These observed differences showed that slow-walking individuals rely on activation of the nonlesioned hemisphere and contraction of the nonparetic leg to achieve cortical drive to the paretic leg, which is different from cortical responses observed in faster walking stroke participants and able-bodied controls.

Cortical asymmetry indices during nonparetic leg contraction

All slow walking participants in this study had negative AIs, indicating that the paretic TA had a lower motor threshold than the nonparetic TA during the nonparetic TA contraction condition. This occurred despite targeting the nonparetic TA by positioning of the TMS coil and “priming” the nonparetic TA muscle through precontraction, which typically increases responses in able-bodied individuals (Needle et al. 2013). In contrast, all fast-walking participants had positive AIs, showing a response similar to pilot data from able-bodied individuals. We posit that this heightened excitability to the paretic leg observed in the present study could be due to greater ipsilateral cortical projections from the nonlesioned hemisphere in individuals with poor lower extremity recovery. This explanation is in agreement with the upper extremity model of poor motor recovery post-stroke (Butler and Wolf 2007; Turton et al. 1996; Cicinelli et al. 2003; Harris-Love et al. 2011) and may provide a neurophysiologic explanation for observations of involuntary activation of the paretic limb during homologous nonparetic limb muscle activation (Rose and Winstein 2005; Harris-Love et al. 2005; Tseng and Morton 2010; Kautz and Patten 2005). Inappropriate corticomotor facilitation tied to activation of the nonparetic limb could affect functional use of the lower extremities and may underlie gait impairments resulting in slow walking speeds.

Cortical drive to the paretic leg between conditions

Our MEP₁₀₀ data showed that the corticomotor excitability of the paretic leg in the slow group was *greatest* during the *nonparetic* TA contraction and that the fast group showed *greatest* excitability during the *paretic* TA contraction. These results demonstrate that changes in cortical drive to the lower extremity during the nonparetic TA contraction is different between individuals of high and low-level functional recovery. Our results can support the finding that poor lower extremity outcomes in chronic stroke are related to deficient corticomotor conductivity from the lesioned hemisphere and stronger conductivity from the nonlesioned hemisphere to the paretic leg (Madhavan et al. 2010). Interestingly, the

MEP₁₀₀ results indicate that contraction of the paretic leg fails to facilitate corticomotor drive in slow walking subjects. In the upper extremity, activation of paretic hand muscles was shown to increase transcallosal inhibition of the nonlesioned hemisphere to the lesioned hemisphere in individuals with chronic stroke (Murase et al. 2004). It is possible that the lower extremity in individuals with poor recovery behaves similar to that of the upper extremity (Murase et al. 2004; Cicinelli et al. 2003) and that during activation of the paretic TA, transcallosal inhibition from the nonlesioned hemisphere increased, resulting in no increase in MEP response between the resting and paretic contraction conditions. Increased interhemispheric inhibition may also explain why we did not observe a greater muscle response during rest or paretic muscle contraction conditions in the slow walking group, despite searching for the optimal location for stimulation of the paretic TA on either side of the vertex. Two explanations of these results may be possible: 1) during activation of the nonparetic TA transcallosal inhibition decreases (Murase et al. 2004), which, despite targeting of the ipsilateral hemisphere and nonparetic TA, allowed for the magnetic stimulation current at high intensities reaching the contralateral hemisphere to facilitate the MEP response in the paretic leg or 2) ipsilateral projections from the nonlesioned hemisphere may be present in individuals with poor lower extremity recovery (Turton et al. 1996; Cicinelli et al. 2003; Harris-Love et al. 2011) and increased activation of the nonlesioned hemisphere that occurs with nonparetic leg facilitation had a facilitory effect on the MEP response in the paretic leg. Following injury, maladaptive cortical remapping may occur in a subgroup of the stroke population. This may cause activation of the nonlesioned hemisphere and contraction of the nonparetic leg (Murase et al. 2004) to have a facilitory effect on the paretic leg, contributing to poor lower extremity recovery.

In the presence of lost function following brain injury, one of the most common and consistent observations is that individuals develop compensatory strategies to perform daily activities (Kleim and Jones 2008; Harris-Love et al. 2011). Those individuals most involved may have shown decreased reliance on the paretic limb and increased reliance on the nonparetic limb, which has been shown to be related to major neuronal reconstruction and growth in the lesioned and nonlesioned hemispheres following unilateral cerebral injury (Adkins et al. 2004). Even in able-bodied individuals, coupling immobilization and non-use of one extremity with heavy reliance on the contralateral extremity for functional tasks will result in hemispheric imbalances of cortical excitation and inhibition (Avanzino et al. 2011). Results of the present study support the hypothesis that slow-walkers may undergo neuronal changes making them unable to differentially activate the paretic and nonparetic TA muscles during an isometric contraction through similar mechanisms. Previously, TMS measures of the TA obtained during voluntary dorsiflexion were found to be identical to those obtained during the swing phase of walking in able-bodied adults (Capaday et al. 1999). If maladaptive cortical responses observed during activation of the nonparetic TA in the present study and inability to differentially activate muscles of the paretic leg continued during ambulation, this could contribute to atypical interlimb relations and altered kinetics and kinematics leading to dysfunctional gait and slowed walking speed (Sousa et al. 2013). If slow walkers were able to improve cortical responses to the paretic TA, it is conceivable that these changes in corticomotor behaviours would translate to improvements in lower extremity function for these individuals.

Limitations

Due to the case-control design of the present study, it cannot be determined if observed cortical differences between the fast and slow walking groups existed prior to recovery of ambulation or if differences in functional recovery of walking contributed to different neurophysiologic mechanisms of cortical plasticity. Because of the anatomy of lower extremity muscle representation within the motor cortex, it is improbable that one hemisphere can be stimulated in isolation. Thus, it is possible that observed increased responses in the paretic TA during the nonparetic TA contraction in the slow walkers could be a consequence of increased excitability of the contralateral hemisphere or disinhibition of the ipsilateral hemisphere. Although the “hotspot” locations for each muscle were consistently found to be on the contralateral hemisphere, slight variability in coil placement between the two hemispheres could have influenced the magnitude of corticomotor excitability differences between limbs within a subject and magnitude of corticomotor excitability between subjects. For example, if coil placement of the nonparetic TA hotspot on the nonlesioned hemisphere was closer to the vertex, then this could more easily induce MEPs within the paretic TA through stimulation of the lesioned hemisphere, thus decreasing the magnitude of motor threshold difference between limbs and causing the asymmetry index to be lower than if the coil were positioned more lateral to the vertex. Differences in coil placement could also contribute to the high intersubject variability of corticomotor excitability measures observed in the present study. Future studies using fMRI techniques could distinguish spatial locations within the cortex that are active during nonparetic limb contraction and help in the interpretation of these results. It is possible that the participants who were unable to produce visible voluntary muscle contractions were not contracting their TA muscle at a comparable effort to other participants (i.e. 15%), which may have influenced the results. It should be acknowledged that other factors independent of stroke that were not measured in the present study can affect gait speed and corticomotor excitability such as white matter hyperintensities and cerebral perfusion (Murray et al. 2010; Sorond et al. 2011). Relatively small sample sizes used in the present study require caution when generalizing to larger post-stroke populations. Finally, it should be noted there was a large difference in the walking speeds between groups, with no participants within the middle range of gait speeds represented in this study. Future research is needed to investigate the cortical behaviors of individuals in this middle speed range.

Conclusions

The findings of this study show that, similar to the upper-extremity, the normal balance of cortical excitability to the lower extremity is altered in the most affected individuals post-stroke. This atypical cortical drive is dependent on activation of the nonlesioned hemisphere during volitional contraction of the nonparetic leg. This suggests that improvements in atypical cortical drive may lead to improved gait speeds. Novel rehabilitation strategies that have been shown to enhance corticomotor input from the lesioned hemisphere, decrease corticomotor input from the nonlesioned hemisphere and improve corticomotor asymmetry between limbs in the upper extremity, such as constraint induced movement therapy (Taub and Morris 2001) and functional electrical stimulation (Sasaki et al. 2012; Shin et al. 2008), could potentially improve lower extremity motor function through similar mechanisms.

Future research investigating the effectiveness of such rehabilitation strategies in promoting positive changes in patterns of corticomotor excitability within the lower extremity could empower clinicians to implement therapies that target individual deficits and ultimately lead to improvements in functional ambulation.

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Highlights

- Poor walking recovery following stroke is associated with enhanced cortical drive to the paretic leg during activation of the nonlesioned hemisphere and contraction of the nonparetic leg.
- Neurophysiologic mechanisms that produce the inability to differentially enhance cortical drive to the paretic and nonparetic legs may underlie post-stroke gait impairments.
- Rehabilitation strategies that promote corticomotor balance to the paretic and nonparetic legs could lead to improved walking recovery.

Figure 1. Sample stimulus-response curve fitted to raw data from peak-to-peak MEPs. Motor threshold and MEP₁₀₀ measures are indicated.

Figure 2.

AI versus Walking Speed. The left panel shows the relationship between AI and walking speed ($p < .01$). The right panel shows the difference in AI mean with standard error between fast and slow walking groups. A significant difference in AI between groups is signified by asterisks (*) at $p < .01$.

Figure 3.
Example raw paretic TA MEP₁₀₀ data from a subject in the fast group (left) and a subject in the slow group (right) is shown for the resting (fast: 0.380, slow: 0.287), paretic contraction (fast: 0.738 slow:0.361), nonparetic contraction (fast: 0.273, slow: 0.630).

Figure 4.

Paretic MEP₁₀₀ during each condition. Presented are the mean and standard errors for each condition. Differences were observed in the slow group between MEP₁₀₀ during the nonparetic contraction and paretic contraction condition as well as the resting condition. Differences were observed in the fast group between MEP₁₀₀ during the paretic contraction and the nonparetic contraction condition as well as the resting condition. A significant difference in paretic TA MEP₁₀₀ is signified by asterisks (*) at $p < .01$.

Figure 5. Changes in P TA MEP₁₀₀ between paretic and nonparetic contraction conditions for the fast vs. slow walkers. Presented are the mean and standard errors for each group. A significant difference for change in MEP₁₀₀ between fast versus slow walkers is signified by asterisks (*) at $p < .01$.

Table 1

Subject (N=18) Characteristics and TMS Results

Subj.	Age (yrs)	Stroke Etiology	Time Since Stroke (mo.)	P Side	Gait Speed (m/s)	AI	Paretic MEP ₁₀₀ (avg.)		
							NP Contr.	P Contr.	Rest
S155	54.2	ischemic	96	L	1.16	0.102	0.52	0.655	0.570
S368	70.7	hemorrhagic	20	L	1.44	0.240	0.208	0.549	0.397
S400	78.0	ischemic	102	L	0.94	0.122	0.367	0.388	0.287
S014	63.5	ischemic	95	R	1.92	0.212	0.070	0.256	0.111
S436	61.5	ischemic	83	R	1.01	0.086	0.855	0.939	0.851
S432	54.0	ischemic	18	L	1.13	0.259	0.199	0.226	0.092
S407	61.5	ischemic	20	L	1.13	0.042	0.323	0.342	0.211
S071	47.6	ischemic	45	L	0.84	0.227	0.015	0.262	0.092
S546	55.0	ischemic	17	R	0.90	0.142	0.018	0.119	0.013
S549	62.0	ischemic	51	L	1.00	0.235	0.358	0.447	0.102
S369	59.1	ischemic	12	L	0.18	-0.236	0.039	0.011	0.019
S383	48.7	ischemic	84	R	0.26	-0.502	0.411	0.277	0.187
S313	62.4	ischemic	62	R	0.32	-0.053	0.723	0.501	0.583
S037	65.4	ischemic	274	L	0.32	-0.260	0.071	0.053	0.053
S287	63.4	ischemic	9	L	0.09	-0.410	0.129	0.102	0.003
S294	55.1	ischemic	12	R	0.45	-0.147	0.16	0.032	0.038
S575	77.0	ischemic	7	L	0.40	-0.043	0.158	0.016	0.027
S006	65.0	ischemic	17	L	0.43	-0.201	0.503	0.126	0.068