Impaired Muscle Phasing Systematically Adapts to Varied Relative Angular Relationships during Locomotion in People Post-Stroke

Laila Alibiglou$^{1,2}$ and David A. Brown$^{1,2,3}$

$^1$Department of Physical Therapy and Human Movement Sciences, Northwestern University
$^2$Interdepartmental Neuroscience Program (NUIN), Northwestern University
$^3$Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, Northwestern University

Running header: Bilateral limb phase relationship and paretic muscle phasing

Corresponding author:
Laila Alibiglou, PT, PhD
Department of Physical Therapy and Human Movement Sciences
Feinberg School of Medicine, Northwestern University
645 North Michigan Avenue
Suite 1100
Chicago, Illinois 60611
Email: l-alibiglou@u.northwestern.edu
Phone: (312) 503-4417
Fax: (312) 908-0741
After stroke, hemiparesis will result in impairments to locomotor control. Specifically, muscle coordination deficits, in the form of inappropriately phased muscle activity patterns, occur in both the paretic and non-paretic limbs. These dysfunctional paretic muscle coordination patterns can adapt to somatosensory inputs and also, the sensorimotor state of non-paretic limb can influence paretic limb. However, the relative contribution of interlimb pathways for improving paretic muscle activation patterns in term of phasing remains unknown. In this study, we investigated whether the paretic muscle activity phasing can be influenced by the relative angular spatial relationship of the non-paretic limb by using a split-crank ergometer, where the cranks could be decoupled. Eighteen participants with chronic stroke were asked to pedal bilaterally during each task while surface EMG signals were recorded bilaterally from four lower extremity muscles (vastus medialis, rectus femoris, tibialis anterior, and soleus). During each experiment, the relative angular crank positions were manipulated by increasing or decreasing their difference by randomly ordered increments of 30° over the complete cycle (0° (in phase pedaling), 30°, 60°, 90°, 120°, 150°, 180° (standard pedaling), 210°, 240°, 270°, 300°, 330° out of phase pedaling). We found that the paretic and non-paretic muscle phasing in the cycle systematically adapted to varied relative angular relationships and this systematic relationship was well-modeled by a sinusoidal relationship. Also, the paretic uniarticular muscle (vastus medialis) showed larger phase shifts compared with biarticular muscle (rectus femoris). More importantly, for each stroke subject, we demonstrated an exclusive crank angular relation that resulted in the generation of more appropriately phased paretic muscle activity. These findings provide new evidence to better understanding of the capability of impaired nervous system to produce a more normalized muscle phasing pattern post-stroke.
Hemiparesis is a major consequence of stroke and contributes significantly to the motor disability and compromised quality of life of stroke survivors. Post-stroke hemiparesis can affect limb movement coordination during walking (O’Sullivan and Schmitz 1999; Moore et al. 1993; Wagenaar 1990; Kwakkel and Wagenaar 2002; Nakamura et al. 1988; Bayat et al. 2005) and pedaling behaviors (Brown and Kautz 1998, 1999; Kautz and Brown 1998; Brown et al. 1997). Following cerebral stroke, the temporal ordering of muscle activity during walking is often disrupted, through either impairments that originate in the central control of the phasing of muscle activity, or through the development of compensatory neuromuscular strategies (Den Otter et al. 2007). Amongst the more common muscle activation abnormalities found in hemiparetic gait are the absence or reduced amplitude of specific components of the muscle activation pattern (Perry 1993; Burridge et al. 2001), the prolongation of existing bursts of muscle activity during the stance phase (Shiavi et al. 1987; Hirschberg and Nathanson 1952), phase-advanced activation of transition muscles, those that shorten during transitions between flexion and extension, and phase-delayed activation of power producing muscles during pedaling (Kautz and Brown 1998). Nevertheless, these phasing abnormalities can have the same or different underlying mechanisms.

Evidence from animal (for review, see Duysens et al. 2000) and human studies have suggested that the central nervous system uses multiple somatosensory signals, including limb loading and limb position (af Klint et al. 2010; Grey et al. 2007; Mazzaro et al. 2006; Musselman and Yang 2007; Sinkjaer et al. 2000; Stephens and Yang 1999; Yang et al. 1998), to generate and regulate locomotor muscle activity patterns during walking. In efforts to understand the underlying mechanisms of bilateral control of muscle activity pattern during locomotion, several
studies have been implemented to perturb one leg and observe the generated muscle responses in
the contralateral leg. For example, perturbations to one leg evoked a coordinated response of
muscle activity with the same latency in both legs during stance and locomotion (Berger et al.
1984; Dietz et al. 1989).

Furthermore, muscle activation patterns from neurologically healthy human subjects
during pedaling showed that neuronal interlimb coupling affects muscle activation and
coordination patterns (Ting et al 2000; Ting et al 1998). For example, in a pedaling study of
stroke survivors, it was demonstrated that non-paretic leg activity reinforces and exaggerates
abnormal paretic muscle phasing (e.g. prolonged excitation of vastus medialis) and as a result,
the motor coordination of the paretic leg is more impaired during bilateral than unilateral
locomotor activity (Kautz and Patten 2005). Also, Kautz and colleagues found that unilateral
pedaling induced a complete pattern of rhythmic alternating muscle activity in the non-pedaling
(either paretic or non-paretic) leg of stroke survivors (Kautz et al. 2006). Thus, they suggested
that interlimb pathways may be responsible for a substantial portion of the paretic leg locomotor
output. All of these findings confirm the idea that the interlimb pathways are likely to contribute
to human bipedal locomotion (Dietz 2002a; Zehr and Duysens 2004).

It is already established that dysfunctional paretic coordination patterns can adapt to new
somatosensory inputs, for instance changes in the speed, direction or limb loading during
movement (Reisman et al. 2007; Schindler-Ivens et al. 2004; Brown and Kautz 1998, 1999;
Brown et al. 1997). Sensory influences originating from movement of the non-paretic limb onto
control of the paretic limb motor activity have been reported (Kautz and Patten 2005). Also, it is
well established that the sensorimotor state of one limb can influence another limb (Ting et al.
1998) and therefore, bilateral somatosensory inputs make an important contribution to interlimb
coordination patterns following stroke. Recent split-belt treadmill studies in people post-stroke suggest that the impaired nervous system is still capable of producing an appropriate interlimb coordination and also, it can store the new improved interlimb relationships temporarily (Reisman et al. 2007). However, the relative contribution and importance of interlimb pathways for modifying abnormal muscle activation patterns in terms of phasing is less clear.

Recently, we showed that muscle phasing can be systematically influenced by interlimb pathways and also, the relative angular position of limbs can affect muscle phasing during a dynamic pedaling task (Alibiglou et al. 2009). Based on our previous findings in neurologically non-impaired subjects, in this study, we sought to investigate the extent to which abnormal muscle activity phasing in the paretic limb can be influenced by the relative angular position of the non-paretic limb. The main goal of this experiment was to alter the arrival timing of afferent inputs from the non-paretic leg onto the paretic leg and determine how the abnormal muscle phasing adapts during a bilateral cyclical locomotor task.

We were interested in linking the results from our previous experiment involving non-impaired subjects (Alibiglou et al. 2009) to possible responses in the stroke population, regarding differences between biarticular and uniarticular muscles, and between flexor and extensor muscles, when responding to altered relative angular position of the limbs. According to our previous results, we hypothesized that the paretic muscle phasing in the cycle would systematically adapt to varied relative angular position of limbs and that these phasing adaptations would manifest differently in uni- versus biarticular muscles and in flexor versus extensor muscles.

During locomotion, muscle function is thought to be divided into two specific sets of functional muscle groupings (uni- and biarticular) with different roles (Jacobs and van Ingen
There is evidence that uni- and biarticular muscles might be controlled or behave differently following cerebral stroke. For instance, in a forward-backward pedaling study, Schindler-Ivens et al. (2004) observed phase-advanced activity in backward versus forward pedaling in paretic uniarticular muscles, whereas the corresponding neurologically intact muscles showed little to no phasing change. Also, it has been suggested that the proprioceptive afferent information continuously modulates the activity of extensors with their antigravity function during gait, whereas the flexor activation is more controlled by central inputs (for a review see Dietz 1992).

Finally, it is not known if the impaired nervous system post-stroke is capable of generating a more appropriate pattern of muscle activity phasing. Thus, another purpose of this study was to investigate the effect of relative angular position changes on inducing phasing patterns that resemble those reported to be generated by the non-impaired nervous system (Kautz and Brown, 1998). Preliminary findings of this study were published in abstract form (Alibiglou et al. 2008).

METHODS

Subjects

Participants in this study were eighteen individuals [12 men, 6 women; age: 59±11 (SD) years] who had sustained a single, unilateral, cortical or subcortical stroke and more than one year post-ictus [72±55 (SD) months] prior to the study and who had experienced at least a residual lower limb paresis (Table 1). The walking ability of the hemiparetic subjects in this study ranged from independent ambulatory without any assistive devices to independent walking with assistive devices (only cane). Also, they were selected if they could tolerate sitting on the bicycle seat for
at least 2 hours. Nine of the hemiparetic subjects had left-side involvement, and nine had right-side involvement. Subjects were excluded if they had other neurological conditions, severe cognitive or affective disorders, expressive or receptive aphasia, severe concurrent medical problems (e.g. severe cardiac disease, history of poorly controlled brittle diabetes, active cancer etc), orthopedic conditions affecting the legs, or history of hip or knee replacement. This study was approved by the Institutional Review Board at Northwestern University.

**Experimental Apparatus**

A custom-made, split-crank, bicycle ergometer with instrumented pedals, consisting of a seat with a backrest and a motor driven crank was used for this study (Rogers et al. 2004). Participants were secured to the backrest with nylon straps, and shoulder supports were used to further stabilize the trunk, confining movement to the legs during all tasks. Clipless style pedals with straps allowed the subjects to maintain a rigid connection between the feet and pedal during experiments. The entire ergometer was attached to a hydraulic tilt mechanism that was used to position the backboard at 25° from horizontal to assure seating comfort during all experimental conditions. The ergometer had a split-axle design with a detachable coupling mechanism. The between-axle phase alignment was adjustable, allowing the limbs to be coupled in 15° off-sets from fully anti-phased (standard pedaling) to in-phase relationships while motor driven control was maintained. Three optical encoders (BEI Model EX116-1024-2), one at each pedal spindle and one coupled to the right crank, provided measurements of the crank and pedal angles with an accuracy of ±0.3°. Pedaling velocity was controlled by an electric motor (8:1 gear reducer, 10 hp with flux vector drive; model SV3000, Seco Electronics, Lancaster, SC) and was kept constant (40 revolution/min) for all subjects and conditions. This velocity was chosen because a previous
study in our lab had shown that for an imposed velocity of 40 rpm, the motor can accurately regulate actual crank speed despite large applied forces (40.5 ±0.8 rpm) (Rogers et al. 2004).

The control of crank velocity resulted in the motor providing mechanical isolation of the two limbs even during the bilateral pedaling task such that neither leg influenced the velocity profile of the cranks. This critical feature of the apparatus allowed us to mechanically decouple legs in each pedaling task. Consequently, each leg separately went through the same cycle kinematic trajectory across all conditions (a fundamental characteristic of our experimental design) regardless of effort level or single limb force output, and the only thing that was experimentally manipulated was the relative angular position of the legs. In addition, because the motor-driven crank design does not allow us to control workload directly, visual feedback of pedal forces was used to assure that effort levels were similar between conditions (see below).

**Recordings**

Bipolar silver surface electrodes (DelSys, 10 mm length, 1 mm width, 1 cm interelectrode distance) were used to record EMGs from four muscles bilaterally (8 muscles total): vastus medialis (VM), rectus femoris (RF), tibialis anterior (TA), and soleus (Sol). Standard skin preparation was applied prior to the application of bipolar silver surface electrodes. EMG signals were amplified with a gain of 10 at the electrode site before remote differential amplification (common mode rejection ratio: 92 dB, gain range: 100–10,000 times, frequency response: 20–450 Hz) and low-pass filtering (500 Hz, custom-designed filter). The digital optical encoder and force transducer signals were converted to analog with a D/A converter module before sampling. Then all signals were sampled at 1,000 Hz via a 12-bit A/D converter (National Instruments) and Labview software. The timing of EMG collection was synchronized with the acquisition of position data from the crank and pedal optical encoders.
The subjects were asked to pedal with moderate effort, bilaterally, at 12 randomly assigned trials of pedaling at different relative angular relationships with respect to the right leg [0° (in-phase); 30, 60, 90, 120, 150, and 180° (typical standard pedaling); and 210, 240, 270, 300, and 330°]. During each task, the cycle ergometer motor rotated the legs in the forward direction at the constant velocity of 40 rpm (see Fig. 1 – middle section for schematic).

**Experimental Paradigm**

Subjects were instructed to assist the motor actively by pedaling the crank in a forward direction with a moderate amount of effort using both legs. Pedal forces were monitored throughout the pedaling cycle, using tri-axial force transducers in each pedal (Delta 660, ATI-IA, Garner, NC). Bar graphs with real-time pedal force were displayed as visual feedback to ensure that subjects used both legs actively. All sessions began with the standard (nominal 180° out of phase) pedaling task. While asking subjects to “pedal with moderate effort,” their preferred peak force was determined during the initial standard pedaling task. This force value was used as the preferred effort level because pedaling at the standard relative angular position of limbs (180°) was a well-known task (not a novel task) for all subjects, and theoretically both legs should generate similar level of forces during this task. Also, all EMGs’ phasing shifts were later calculated relative to this position. The goal range of force was set at the preferred level ±10%, indicated by error bars on the computer screen. Then for every pedaling task, the pedal forces were monitored and subjects were given feedback to keep approximately the same peak force output that they had produced with the standard pedaling task. At each angular relationship condition, data were collected for 30 s at a rate of 1,000 Hz to ensure ≥20 complete crank revolutions in a steady state. To minimize the possible effects of fatigue, all subjects were
provided a minimum of 30 s rest between trials and were given adequate rest periods if further recovery was needed.

**Data processing**

This study focused on muscle activity phasing, or the relative bursting of muscle activation with respect to the crank angle in pedaling at different relative angular relationships between the paretic and non-paretic leg of people with stroke. First, to compare muscle activity at the same point in the pedaling cycle for every crank revolution, we rectified the EMG signals and referenced them to the crank position in 1-degree increments. Data that were sampled within any 1° increment were averaged and assigned to the crank position that represented the middle value of the range. Next we integrated the EMG signals (in volts) throughout every pedaling cycle. For each task, the integrated EMGs were averaged across 20 crank cycles. During this process, left and right legs (or non-paretic and paretic legs) were analyzed independently. The EMG profiles were inspected visually offline and any records showing involuntary activation of the recorded muscles (e.g. clonic EMG activity) were excluded from the analysis. Also, if EMG activity was inordinately continuous throughout the cycle, but where no obvious amplitude modulation occurred (i.e. when EMG was ‘tonic’), the data was not included in the analysis because it wasn’t mathematically possible for our custom-designed program to accurately find a maximal cross-correlation value.

To compare the phasing of EMGs in pedaling at various relative angular positions, first all EMG profiles were smoothed with a fourth-order, zero-lag, low-pass Butterworth filter with a cutoff frequency of 25 Hz. Then, we cross-correlated (Fig. 2) each full-wave smoothed EMG signal from different experimental conditions to the EMG signal of the same muscle (at the same side) in the nominal 180° phase relationship using a custom-designed program written with
Matlab (R2009a) software. This cross-correlation process has been described previously (Alibiglou et al. 2009). In brief, we considered two processed EMG profiles of the nominal 180° angular relationship and that of another experimental condition (Fig. 2.A). The complete processed EMG signal of each experimental condition was displaced forward and backward in 1° increments through the entire EMG profile of nominal 180° (Fig. 2.B). Correlations were taken and saved at every step. Then the lag at which the highest correlation occurred between EMG profile of nominal 180° and the compared experimental condition was deemed as the phase shift for that specific position. The sign of this phase shift was considered positive or negative relative to EMG profile of nominal 180°. Positive values for the phase shift indicate advanced phasing, whereas negative values indicate delayed phasing. This gave us a value for the number of degrees of phase change that occurred for that muscle within that angular relation condition relative to the nominal pedaling (180°). The group averages of phasing changes at each relative angular relation were then calculated for each muscle separately. Phase change magnitude versus angular relation were plotted and then fitted with a sine wave (Fig. 2. C) by using a program that applied the Levenberg–Marquardt algorithm (OriginPro 8 software). So we were able to compare sine wave parameters (amplitude, phase lag and period) of the fitted sine waves to find the relationships between EMGs’ phase shifts versus limb angular differences for different muscles during our manipulations. Note that in this study, the sine wave represents the phase shift of muscle activity from the nominal 180° position at each relative angular crank position. Each point along the sine wave (the amplitude of the sine wave at each relative crank position) represents the amount of EMG phase shift that yielded the greatest cross-correlation coefficient for that condition. Positive values for the amplitude represent an advanced phase shift relative to nominal 180° position, whereas negative values express the delayed phasing shift relative to
nominal 180°. The period of each sine wave was also measured because it helped us to calculate the frequency of each sine wave, which suggests whether the muscles are controlled by oscillators acting at the same or different frequencies. Another parameter of sine function was the phase lag that represents a “shift” of the sine wave relative to a zero phase shift. For example, in the case of our studies, existence or nonexistence of a phase difference between the sine waves of different muscles during the same experimental task could indicate whether a pair of central oscillators was out of phase or in phase with each other.

For each subject, calculated phase shifts, with 1° resolution, were plotted and fitted with a sine wave function for both, the paretic and the non-paretic, limbs. To test whether changing the relative angular position of limbs produced different phase shifts in the paretic versus non-paretic leg of people with stroke, we compared the parameters of the sine waves fitted to all recorded muscles, averaged across all subjects, of paretic leg to non-paretic leg.

To compare the paretic leg’s muscles to the non-paretic leg, we normalized the phasing changes of the paretic limb of all subjects to the right limb and those changes of the non-paretic limb to the left limb, whether subjects suffered from left- or right-hemispheric strokes. This normalization was applied because the fitted sine waves showed that the phase-advanced activity in the ipsilateral leg was coincided with phase-delayed activity in the contralateral leg and vice versa. Since half of our subjects suffered from right and half of them from left hemispheric stroke, averaging the parameters of fitted sine curves from paretic or non-paretic limbs without normalization could potentially produce inaccurate and misleading results. Then a two-tailed paired sample t-test was used to determine whether there was any difference between the corresponding muscles’ phasing responses of the paretic and non-paretic leg to the same angular crank relation condition. We used a $p$ value of $<0.05$ to test for significance.
To find out the extent to which uniarticular (VM) versus biarticular muscle (RF) and flexor (TA) versus extensor (Sol) muscle phasing responses to relative angular phasing manipulations were similar, we compared their sine waves parameters with two-tailed paired sample t-test. We used a p value of <0.05 to test for significance.

Also, we were interested to ask whether there is a relative angular position of limbs that can most ideally modify impaired paretic muscle phasing, and generate more optimal paretic muscle phasing. To address this question, we first cross-correlated each EMG profile of paretic VM from different relative angular positions of each stroke survivor to the representative averaged EMG profile of a previously reported set of intact subjects’ VM in the nominal 180° condition (Alibiglou et al. 2009). Then, the relative angular position at which the highest correlation occurred between compared EMG profiles was considered as “the optimal corrective phase shift” for that stroke survivor. Within each subject, we compared the averaged EMG percent of the end of the downstroke/beginning of upstroke quadrant at nominal 180° condition of each stroke survivor to the corresponding quadrant at the optimal corrective angular condition of the same subject. For this analysis, a two-tailed paired sample t-test was performed. All statistical analyses were performed using OriginPro 8, and the p value was set at 0.05.

RESULTS

Comparison of sine wave parameters representing phase shifts of each muscle

Previously, we had shown in neurologically healthy individuals that the timing of the EMGs shifted earlier and later in the cycle when the relative angular position of limbs was changed (Alibiglou et al. 2009). Similar to those findings, Figure 1 (VM and RF only displayed) shows that the onsets of EMG activities of the paretic and the non-paretic limb were also delayed or advanced as a consequence of changing the relative angular position of limbs. These changes
were evident across all recorded muscles of both the paretic and the non-paretic limbs of all participating subjects with stroke. Table 2 presents the group averaged sine wave parameters (phase lag, amplitude, and period) of each measured muscle from the paretic and the non-paretic leg. The adjusted \( r \)-squared values in this table confirm that these sine waves were well fitted to the group-averaged data.

The fitted sine waves showed phase-advanced activity in relative angular crank relations where the ipsilateral leg (either paretic or non-paretic) was leading contralateral leg movement and phase-delayed activity in experimental relations where the ipsilateral leg was following contralateral leg movement. As shown in Figures 3, the phase lag and amplitude of sine waves fitted to each muscle’s phasing changes varied between different muscles and also, between the paretic and the non-paretic legs. Between-group comparisons (paretic vs. non-paretic) revealed that the amplitude of fitted sine waves of VM, RF and Sol of the paretic limb were significantly greater compared with the non-paretic limb (\( p<0.05 \)). But the TA muscle on the paretic and non-paretic legs demonstrated relatively similar phasing behavior at each angular crank relation and there was no significant difference (\( p>0.05 \)) between the amplitude of its sine waves. Comparing the phase lags of the paretic and the non-paretic fitted sine waves revealed that the Sol was the only muscle that the phase lags of its paretic and non-paretic sine waves differed significantly (\( p<0.05 \)).

**Comparison of the uniarticular (VM) and biarticular (RF) muscle activity phase changes**

Figure 3 shows the comparison of group averaged fitted sine waves for a representative biarticular (RF) and uniarticular (VM) extensor muscle crossing the knee in both non-paretic (A) and paretic (B) limbs of stroke survivors. In the paretic lower extremity (Fig. 3.B), the amplitude of the fitted sine wave in the uniarticular extensor muscle (VM) was significantly greater than
biarticular extensor muscles (RF) \( p<0.05 \), while, in the non-paretic lower extremity (Fig. 3.A), there was no significant difference between the amplitude of the fitted sine waves of the uniarticular extensor muscle (VM) and the biarticular extensor muscle (RF; \( p>0.05 \)). These results were different from the previous observations in neurologically healthy individuals (Alibiglou et al. 2009) that had shown the magnitude of phasing changes in biarticular extensor muscle (RF) was significantly greater than those of uniarticular extensor muscle (VM). When we compared other sine wave parameters (phase lag and period) of the uni- and biarticular muscle, we found no significant difference in the paretic side and also, in the non-paretic side \( p>0.05 \).

**Comparison of the ankle extensor and flexor muscle activity phase changes**

We used a two-tailed paired sample \( t \)-test to compare responses to changes in relative angular crank position, in the form of the derived sine wave parameters, with the major uniarticular ankle flexor (TA) and one of its major uniarticular extensor (Sol) muscles. In the paretic leg, we observed that the phase lags of the fitted sine waves differed significantly \( (p<0.05) \) between Sol and TA (Fig. 3.D) whereas we found no significant difference between the amplitudes of the fitted sine waves \( (p>0.05) \). In the non-paretic limb (Fig. 3.C), the amplitude of sine wave in Sol muscle was significantly lower compared with TA \( (p<0.05) \).

There was no significant difference between the phase lags of non-paretic TA and Sol fitted sine waves \( (p>0.05) \). Furthermore, we didn’t find any significant difference between the period of these muscles’ fitted sine waves in both paretic and non-paretic lower extremities \( (p>0.05) \).
Relative angular position of limbs that generates optimal improved EMG phasing in the paretic limb

We tested whether changing the relative angular position of limbs could shift the paretic VM muscle phasing to a more optimal (i.e. normal) phasing. First, we validated the result, previously published by Kautz and Brown (1998), that the paretic VM phasing is characterized by an increased percentage of EMG activity occurring during the end of downstroke/beginning of upstroke portions of the pedaling cycle (Fig. 4.A). As shown in Figure 4.B and C, our results revealed that, at the optimal corrective angular position, the percentages of paretic VM activity during the impaired quadrant of a pedaling cycle (i.e. end of downstroke/beginning of upstroke) were significantly reduced compared to the nominal 180° relative angular crank condition [11.27±1.38 (SE) vs. 14.13±2.09 (SE) respectively; \( p<0.05 \)]. In addition, the amplitude of VM EMG (Fig. 4.A and B) was in fact reduced for the compiled optimally corrected EMG patterns compared with the data from the nominal 180° phasing condition [nominal 180° condition: 0.70±0.5 (SD) mV vs. optimal corrected condition: 0.47±0.38 (SD) mV, \( p<0.05 \)]. This result implies some potential trade-off between the control of EMG phasing and amplitude. More importantly, we found that the “optimal corrective angular position” was different across all subjects (Fig. 4.D) and indeed, there is no consistent relative angular position of limbs that can modify the impaired paretic muscle phasing in all subjects post-stroke.

DISCUSSION

Recently, we showed that the phasing of the muscle activity of the lower limbs can be systematically influenced by the relative angular relationship of the limbs in neurologically healthy individuals. In these individuals, manipulation of somatosensory inputs by changing the relative angular position of limbs caused muscle activity phasing changes that were either
delayed or advanced, dependent on the relative angular position of the two cranks (Alibiglou et al. 2009).

In the present study of people with stroke, we found that manipulating the angular relation of the cranks in a pedaling task can cause paretic and non-paretic muscle activity phasing changes that are either delayed or advanced, dependent on the relative angular position of the two cranks. Therefore, our main hypothesis that the paretic and non-paretic muscle phasing in the cycle systematically adapts to varied relative angular relationships in individuals with stroke was supported. More importantly, the magnitudes of these changes were asymmetrical about the paretic and non-paretic legs. We found that the paretic uniarticular muscle (VM) showed significantly greater phasing responses compared with biarticular muscle (RF). Also, our results revealed that the phase lag of paretic Sol fitted sine wave was significantly smaller than paretic TA fitted sine wave, whereas the amplitude (magnitude of phasing responses) of their fitted sine waves didn’t vary. We demonstrated that non-paretic Sol (ankle extensor) muscle showed significantly smaller phasing responses compared with non-paretic TA (ankle flexor) muscle. These results are in contrast to our previous findings in age- and gender- similar neurologically intact individuals (Alibiglou et al. 2009).

Equally important is the finding that it is possible to systematically modify and shift the paretic muscle phasing to more normal muscle phasing activity by changing the relative angular position of limbs. Here, we demonstrate for the first time, to the best of our knowledge, the potential of specifically altered timing of somatosensory inputs to induce more appropriate motor output in the presence of an impaired nervous system.

Note that because of the apparatus characteristics and our control of pedaling effort, although we changed the angular relation of the cranks relative to each other, the mechanics of...
the task remained invariant for each leg across all conditions (see Methods). Therefore, this critical feature of our design helped us to study neural control strategies without interactions caused by mechanical task constraints. In other words, the mechanics of the task was always the same for each limb and the CNS was not required to modify its controlling strategies for each limb as a result of the relative angular crank relations changes. This setup then allows an extra degree of control than what is afforded with split-belt treadmill experiments and provides a comparative experimental paradigm for investigating interlimb coordination in the post-stroke nervous system (Reisman et al. 2009; Reisman et al. 2007; Reisman et al. 2005; Dietz et al. 2001; Dietz et al. 1994).

Changes in muscle activity phasing patterns post-stroke

In our prior study with neurologically intact subjects, we suggested that the CNS uses a simple sine tuning system for controlling the muscle’s phasing to compensate for relative angular changes of limbs (Alibiglou et al. 2009). Here, our new results in people post-stroke also show that the average of the r-squared values for fitted sine waves (Table 2) was 0.93. This indicates that in people post-stroke similar to intact subjects, the degree of fit of data to the sine wave model was high.

One of our most important findings is that although cerebral lesions cause muscle phasing abnormalities post-stroke, these cerebral lesions do not impair the overall sine tuning system that CNS uses for controlling the muscle phasing in response to relative angular changes of limbs. This result is similar to other previous studies that demonstrated that, even though cerebral structures are damaged and paretic muscle activity phasing is impaired post-stroke, the adaptations to different types of sensory inputs are appropriate in individuals with stroke.
For example in pedaling, when changes were made to the speed (Brown and Kautz 1999), workload (Brown and Kautz 1998), and body orientation (Brown et al. 1997), stroke survivors were able to adapt to these changes, similar to that observed in neurologically intact people.

**Uni- versus biarticular muscle phasing changes in pedaling task post-stroke**

Previously in our study of neurologically healthy subjects, we described that the magnitude of phasing changes in biarticular muscles was significantly greater than those of uniarticular muscles. However, in this study, we have demonstrated that uni- and biarticular muscles behave differently in the paretic and non-paretic limb of people with stroke. In the paretic limb, the tested uniarticular muscle (VM) showed significantly greater phasing changes compared with the biarticular muscle (RF). These results were consistent with a previous pedaling study that has shown that paretic uniarticular muscles are more susceptible to sensory adaptation than paretic biarticular muscles (Schindler-Ivens et al. 2004). Schindler-Ivens and colleagues observed that when pedaling direction was reversed, the paretic VM (uniarticular) muscle activity during backward pedaling was advanced in phase compared with forward pedaling whereas the paretic RF (biarticular) muscle didn’t change its phasing. So, it was suggested that the integration of sensory input may be altered for uni- and biarticular muscles post-stroke.

Based on our findings, we also investigated the possibility that more appropriately phased paretic muscle activity can exist under the appropriate crank angular relation conditions. For most stroke subjects, we found an exclusive crank angular relation that resulted in the generation of more appropriately phased paretic VM activity. This observation supports previous studies that showed that during backward pedaling (Schindler-Ivens et al. 2004) and, also, unilateral pedaling conditions (Kautz and Patton 2005), paretic VM phasing showed reduced muscle
activity during the transition from limb extension to limb flexion. However, these studies indicated that the paretic VM phasing improvement didn’t resemble intact VM phasing since the prolonged nature of the activation still remained, but showed up as early onset of VM activity during the terminal phase of limb flexion. While in the present study, bilateral pedaling at the optimal corrective angular relation for each subject not only shifted the paretic VM phasing to more appropriately phased activation but also reduced the consequent inappropriate terminal phase activity (end of upstroke) (Please see Fig. 4.A and B).

**Flexor versus extensor muscle phasing changes in pedaling task post-stroke**

Another finding of this study is that paretic and non-paretic TA showed similar magnitudes of phasing responses to changes with angular crank relation whereas the magnitudes of phasing changes of paretic Sol were much greater than non-paretic Sol. It had been shown that the corticospinal projections to lower limb motoneurons to the TA muscle are stronger than to the Sol muscle (Brouwer and Ashby 1992; Schubert et al. 1997). It also has been suggested that during walking the corticospinal tract is more closely linked with the segmental neural circuits controlling TA than it is with those controlling Sol (Capaday et al. 1999). These studies suggest that there is a corticospinal control of locomotion in humans (Capaday et al. 1999; Schubert et al. 1997; Petersen et al. 2001). Thus, damage to the CNS, like what happens post-stroke, can cause foot drop by preferentially reducing activation of the ankle flexor muscle (TA) during walking, although activity in the ankle extensor muscles may also be abnormal (Knutsson 1981; Burridge et al. 2001; Dietz et al. 1994). Practically, the corticospinal connections enable the subject to voluntarily circumvent obstacles without losing postural stability (Dietz 2003) and therefore, people with cerebral stroke are not able to do this movement because of abnormal TA activation.
In fact, all of these findings suggest that there is a difference between underlying control mechanisms of TA and Sol muscle.

Based on the observed similarity of the paretic and non-paretic TAs fitted sine waves, and also their likeness to the non-impaired TA fitted sine wave (described previously), we suggest that cortical inputs are less important in modulating muscle activation phasing. Therefore, the muscle timing abnormalities post-stroke are indirectly related to cortical damage and possibly are the direct result of reflex changes at the spinal level or compensatory changes of interlimb pathways.

**Possible underlying neural control schemes**

An important finding of this study is that the impaired nervous system following cerebral stroke is still able to systematically modulate the muscle activity phasing when the spatial relative angular position of legs are altered. This finding indicates that the initial state of the compensatory muscle phasing post-stroke has the potential to become attuned to spatial angular constraints arising from a new bilateral task and therefore, to interlimb position inputs. Similarity of these observations and our recent findings in the intact subjects (Alibiglou et al. 2009) provide new evidence for the importance of interlimb pathways in regulation of the paretic muscle phasing.

Elucidation of interlimb neural coupling mechanisms in humans is difficult because central and peripheral influences cannot be explicitly isolated. However, changes in muscle activation coordination of a leg in bilateral tasks such as gait may be caused by different contralateral and ipsilateral sensorimotor afferents (i.e. load and position sensory inputs). Evidently, these changes are more complicated in the presence of central nervous system impairment. The appropriate adjustment of human walking requires a close coordination of
muscle activation phasing between the two legs (see Dietz 2002b, for a review of the research supporting this point).

Different control mechanisms have been proposed for generation of the appropriate phasing pattern of locomotor bursts in neurologically healthy human. Regarding our findings, a legitimate question is whether the cerebral damage is the main cause of the inappropriate paretic muscle phasing post-stroke. To address this question, first we will discuss some central control theories that are directly or indirectly related to the results of this experiment.

Few mechanisms have been proposed for generating inappropriate intralimb and interlimb muscle activity phasing post-stroke. It has been shown during gait that a perturbation of one leg evokes a purposeful, bilateral response pattern (Berger et al. 1984; Dietz et al. 1986). Because of the short latencies of the EMG responses in these studies, it was suggested that the response measured in the contralateral leg may be mediated by a flexible neural coupling at spinal level (Dietz et al. 1986; for review see Dietz 1992, 2002a). Recently, data from animal studies have suggested that there is a unique phasing and pattern control center in the spinal cord that can receive inputs from different pathways and networks, while the only output that it generates is timing of the locomotor behavior (McCrea and Rybak 2008). According to this contemporary model of central pattern generators, abnormal inputs even from one limb or inappropriate operation of rhythm-generating networks can cause uncoordinated locomotor behavior. In human, study of a patient with spinal cord injury (SCI) has confirmed the presence of the involuntary rhythmic alternating muscle activity in the lower limb while the patient was incapable of generating any muscle activity voluntarily (Calancie et al. 1994). Further, the demonstration of the non-patterned epidural electrical stimulation in people with complete SCI has been shown to induce patterned, locomotor-like bursts of EMG activity and also to elicit
locomotor synergy patterns in lower extremity muscles (Dimitrijevic et al. 1998, Shapkova & Schomburg 2001, Shapkova 2004). These findings suggest that the oscillatory patterns of muscle activity observed during human locomotion are basically generated by CPGs. In studies of both groups (people with stroke and neurologically intact people) we demonstrated a sinusoidal nature of muscle phasing variations. Although the magnitude of phasing changes (amplitude of sine wave) in the paretic and the non-paretic limbs were different for most of tested muscles, both groups of muscles, the paretic and the non-paretic, preserved their sinusoidal pattern of muscle activation phasing in response to alternations of relative angular position of limbs. Our results are consistent with the idea that phasing of the muscle activation during locomotion is controlled by central pattern generators.

Even though locomotor movements are generated centrally, several animal and human studies have shown that somatosensory afferents play a critical role during locomotion, particularly in sculpting the locomotor pattern (Wetzel et al. 1976; Goldberger 1977, 1983; Grillner and Zangger 1984; af Klint et al. 2010; Grey et al. 2007; Mazzaro et al. 2006; Musselman and Yang 2007; Sinkjaer et al. 2000; Stephens and Yang 1999; Yang et al. 1998). In the present study, we manipulated the relative phasing of sensorimotor inputs of one side relative to another side by changing the relative angular crank relations. Put differently, because the intralimb mechanics and trajectory of movement were always the same across all conditions, the ipsilateral side still received consistent sensorimotor state signals from the contralateral side, but these sensorimotor signals arrived at spinal neural networks of the ipsilateral side at different relative phasing from condition to condition. Thus, each limb either paretic or non-paretic had to adapt a new muscle activity phasing to maintain the interlimb coordination strategy needed to perform the desired task at different conditions. These findings clearly confirm the importance of
the presence of both the paretic and the non-paretic somatosensory inputs in generation of locomotor movement.

Evidence from people with stroke (Kautz and Patten 2005; Kautz et al. 2006) and spinal cord injury (Dietz et al. 2002) suggest that locomotor interlimb coordination is strongly influenced by cerebral inputs. However, Reisman and colleagues, in a study of people with cerebral stroke, showed that cerebral regions were less important for peripherally driven locomotor adaptations (Reisman et al. 2007). While it is still unknown if muscle activation abnormalities post-stroke are originating from cerebral lesion or they are indirect consequences of the lesion, we demonstrate for the first time that the muscle timing abnormalities are alterable, even in presence of cerebral stroke. Another controversial finding of this study was very similar phasing changes of TA muscle that we found in the paretic and the non-paretic limb of stroke survivors. As described earlier, it has been suggested that the corticospinal tract is very closely linked with the neural networks controlling TA muscle during locomotion (Capaday et al. 1999). Therefore, we expected to see more dramatic phasing changes in TA compared with other lower extremity muscles following cerebral stroke. Nevertheless, we didn’t find any significant difference between non-paretic and paretic TA. These findings indirectly indicate that cortical areas are not primarily important in controlling interlimb coordination and particularly, muscle activation phasing. This also supports earlier results from studies of people with spinal cord injury that interlimb coordination may not depend on supraspinal inputs (Ferris et al. 2004; Kawashima et al. 2005).

Furthermore, it is presumed that cerebellar damage can lead to clear and consistent abnormalities like a lack of coordination in movement (Bastian 2006) and therefore, cerebellar damage can disrupt interlimb adaptation and coordination (Morton and Bastian 2006). Since the
interlimb coordination is directly related to appropriate muscle activation phasing, thus its
disruption following cerebellar lesion can imply the indirect involvement of the cerebellum in
controlling muscle activation phasing and timing. In our study, participants didn’t exhibit any
cerebellar lesion symptoms and we assumed that they had no damage to cerebellum and their
impairments were limited to cerebral structures. Therefore, this might help to explain that why
the temporal adaptation we observed in this study is similar with adaptation we observed in the
non-impaired individuals prior to this study.

CONCLUSIONS

A central issue for our understanding of how discoordinated locomotion post-stroke can
be improved is the extent to which the impaired nervous system is able to adapt more appropriate
muscle phasing by being exposed to novel somatosensory inputs (like different relative angular
position). Here we found that short term exposures to novel timing of somatosensory inputs are
able to temporarily generate a more normal motor output post-stroke. More importantly, we
found that the proposed sine tuning mechanism that non-impaired CNS uses for modulating the
muscle’s phasing is intact even in presence of cerebral damage. Taken together, the results of
this study have opened the door to a new way of manipulating the contralateral state of the non-
paretic leg so that the paretic leg can potentially recover appropriate phasing of muscle activity.

It is still unknown if short bouts of training at the optimal corrective relative angular position can
results in behaviors that functionally reduce the muscle phasing abnormalities observed post-
stroke. We propose that the central nervous system of people with cerebral lesions is capable of
learning new muscle activation phasing, and applying these adaptations in a functional way to
improve interlimb coordination.
ACKNOWLEDGMENTS

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**FIGURE LEGENDS**

**Figure 1.** Averaged smoothed EMG signals from a representative stroke survivor (S15, LE FM=24) during bilateral pedaling at all 12 different relative angular crank relations. EMG traces from left to right columns correspond to: Paretic RF (black), Non-paretic RF (gray), Paretic VM (black) and Non-paretic VM (gray). Also, schematic view of different angular crank relations in our pedaling tasks has shown between the EMG columns. In all twelve conditions, the right pedal was assumed as the reference side and the relative angular relationship of limbs were determined by calculating the angular distance of left pedal from right pedal in clockwise direction.

**Figure 2.** Illustration of cross-correlation and sine wave fitting techniques used in our study. 

A: represents two averaged smoothed EMG signals of a tested muscle during bilateral pedaling task at 180° (filled black) and 270° (patterned black) relative angular crank positions. B: Cross-correlation technique: the complete processed EMG signal at 270° condition was displaced forward and backward in 1° increments through the entire EMG profile of nominal 180°. At every step, correlations were taken and saved. Then the lag (e.g. M) at which the highest correlation occurred between EMG profile of nominal 180° and 270° condition was deemed as the phase shift for this condition. This process was done for each relative angular position of limbs separately. C: Each lag was then plotted for all twelve relative angular crank relations, and then fitted with a sine wave. Here in C, the “Amp” represents the peak amplitude of the fitted sine wave. The “Period” represents the period of each fitted sine wave and the “Phase lag” represents the angular shift of a fitted sine wave relative to an ideal zero phase sine wave (gray dashed line).

**Figure 3. A and B:** Comparison of group averaged sine waves fitted to: thigh biarticular muscle; RF (black line and filled squares), and thigh uniarticular muscle; VM (gray line and filled triangles) phasing changes in both the paretic (B) and the non-paretic (A) limbs. Positive values for the phase shift indicate advanced phasing, whereas negative values indicate delayed phasing relative to muscle activity at 180°. As shown in B, the magnitudes of phasing shifts are greater for the uniarticular VM muscle compared with the biarticular RF muscle. A shows that the amplitude difference between uni- and biarticular muscle’s phasing shifts were not significant in the non-paretic limb. 

**C and D:** Comparison of group averaged sine waves fitted to: ankle extensor muscle; Sol (black line and filled squares), and ankle flexor muscle; TA (gray line and filled triangles) phasing changes in both the paretic (D) and the non-paretic (C)
limbs. As shown in C, the magnitudes of phasing shifts are greater for the flexor muscle (TA) compared with the extensor (Sol) muscle in the non paretic limb. D shows that there is a significant difference between the phase lags of TA and Sol fitted sine waves in the paretic limb.

Figure 4. A: Comparison of the representative averaged (±SE) EMG profile of intact subjects’ VM (light gray) and of paretic VM of stroke subjects (dark gray) in the nominal 180° condition. The specific quadrant (end of the downstroke/beginning of upstroke) that is usually impaired post-stroke has been enlarged in the inset figure. B: Comparison of the representative averaged (±SE) EMG profile of intact subjects’ VM (light gray) in the nominal 180° condition and of paretic VM of stroke subjects (dark gray) in the optimal corrective condition. The specific quadrant (end of the downstroke/beginning of upstroke) that is usually impaired post-stroke has been enlarged in the inset figure. By comparing A and B, it is clear that the VM muscle phasing has been shifted toward more appropriately phasing at the optimal corrective condition. C: Comparison of average EMG percent of VM at specific quadrant for stroke subjects at nominal 180° condition (gray bars) and at optimal corrective condition (black bars) in 10 degree increments. D: Comparison of average EMG percent of VM of total quadrant for stroke subjects at nominal 180° condition (gray bars) and at optimal corrective condition (black bars). As shown here, there is a significant difference between nominal and optimal condition in the total percent activity of this quadrant. E: shows that the optimal corrective angular crank relation was different across all subjects.

TABLE LEGEND

Table 1. Characteristics of subjects with stroke

Table 2. Group averaged sine wave parameters fitted to each muscle’s phasing changes relative to the 180° angular crank relation condition
Relative Angular Crank Relation (Deg)

A (Non-paretic)

B (Paretic)

RF Adj. $R^2 = 0.88$
VM Adj. $R^2 = 0.95$

RF Adj. $R^2 = 0.91$
VM Adj. $R^2 = 0.96$

C (Non-paretic)

D (Paretic)

Sol Adj. $R^2 = 0.92$
TA Adj. $R^2 = 0.97$

Sol Adj. $R^2 = 0.94$
TA Adj. $R^2 = 0.96$
TABLE 1. Characteristics of subjects with stroke

<table>
<thead>
<tr>
<th>Subject</th>
<th>Hemiparetic side</th>
<th>Gender</th>
<th>Age</th>
<th>Time since Stroke (months)</th>
<th>LE Fugl-Meyer (max=34)</th>
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<td>L</td>
<td>M</td>
<td>57</td>
<td>18</td>
<td>30</td>
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</table>
## TABLE 2. Group averaged sine wave parameters fitted to each muscle’s phasing changes relative to the 180° angular crank relation condition

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Phase lag</th>
<th>Period ($\frac{1}{F}$)</th>
<th>Amplitude*</th>
<th>Adj. R²</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF (P)</td>
<td>20.75±5.4</td>
<td>189.06±8.5</td>
<td>34.00±3.0</td>
<td>0.91</td>
<td>14</td>
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<tr>
<td>VM (P)</td>
<td>7.55±3.2</td>
<td>185.35±4.9</td>
<td>43.49±2.5</td>
<td>0.96</td>
<td>14</td>
</tr>
<tr>
<td>Sol (P)</td>
<td>-20.03±3.6</td>
<td>173.03±5.0</td>
<td>28.08±1.9</td>
<td>0.95</td>
<td>14</td>
</tr>
<tr>
<td>TA (P)</td>
<td>11.38±3.2</td>
<td>184.00±4.9</td>
<td>31.36±1.8</td>
<td>0.96</td>
<td>14</td>
</tr>
</tbody>
</table>

| RF (NP) | 6.74±8.6 | 172.13±6.9 | 16.58±1.7 | 0.89    | 16 |
| VM (NP) | 11.96±5.4| 173.94±4.5 | 15.79±1.0 | 0.95    | 16 |
| Sol (NP)| 5.60±7.4 | 178.64±6.2 | 19.23±1.6 | 0.92    | 14 |
| TA (NP) | 3.28±4.1 | 177.23±3.4 | 28.96±1.3 | 0.97    | 14 |

Values are means ± SE. RF, rectus femoris; VM, vastus medialis; Sol, soleus; TA, tibialis anterior; P, paretic limb; NP, non-paretic limb. N is the number of subjects whose EMG’s sine function for each muscle has been considered for statistical analysis. * Amplitude is the degrees shifted relative to 180° condition. Note that for statistical purposes, all the phase lags of the paretic muscles have been normalized by deducting 180° from their original value.